(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 April 2002 (18.04.2002)

PCT

(10) International Publication Number
WO 02/30860 A2

(51) International Patent Classification[7]: C07C 49/17, 49/245, 49/258, 49/185, A61K 31/12, 31/122, 31/185, 31/21, 31/275, 31/095, 31/33, 31/66, A61P 9/00, C07C 49/82, 49/86, 49/782, 49/215, 49/723, 49/743, 49/747, 49/507, 50/30, 261/04, C07F 9/09, 9/24, 9/44, C07C 69/716, 69/738, 309/24, 309/07

(21) International Application Number: PCT/US01/31872

(22) International Filing Date: 11 October 2001 (11.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/239,232 11 October 2000 (11.10.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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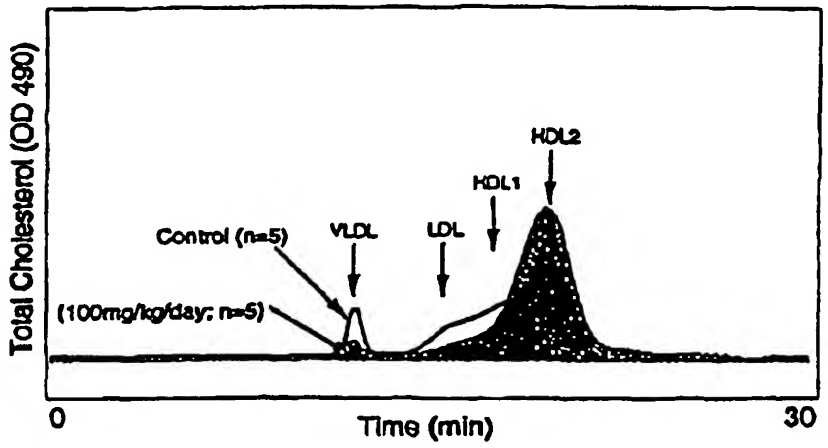
(54) Title: KETONE COMPOUNDS AND COMPOSITIONS FOR CHOLESTEROL MANAGEMENT AND RELATED USES

Effect of One Week of Daily Oral Gavage Treatment with Compound B on Lipoprotein Total Cholesterol in Chow-Fed Male Sprague-Dawly Rats



(57) Abstract: The present invention relates to novel ketone compounds, compositions comprising ketone compounds, and methods useful for treating and preventing cardiovascular diseases, dyslipidemias, dysproteinemias, and glucose metabolism disorders comprising administering a composition comprising a ketone compound. The compounds, compositions, and methods of the invention are also useful for treating and preventing Alzheimer's Disease, Syndrome X, peroxisome proliferator activated receptor-related disorders, septicemia, thrombotic disorders, obesity, pancreatitis, hypertension, renal disease, cancer, inflammation, and impotence. In certain embodiments, the compounds, compositions, and methods of the invention are useful in combination therapy with other therapeutics, such as hypocholesterolemic and hypoglycemic agents.

WO 02/30860 A2

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

KETONE COMPOUNDS AND COMPOSITIONS FOR CHOLESTEROL MANAGEMENT AND RELATED USES

1. Field of The Invention

The present invention relates to ketone compounds; compositions comprising the ketone compounds; and methods for treating or preventing a disease or disorder, such as cardiovascular disease, dyslipidemia, dyslipoproteinemia, a disorder of glucose metabolism, Alzheimer's Disease, Syndrome X, a peroxisome proliferator activated receptor-associated disorder, septicemia, a thrombotic disorder, obesity, pancreatitis, hypertension, renal disease, cancer, inflammation, and impotence. The ketone compounds and compositions of the invention may also be used to reduce the fat content of meat in livestock and reduce the cholesterol content of eggs.

2. Background of The Invention

Obesity, hyperlipidemia, and diabetes have been shown to play a causal role in atherosclerotic cardiovascular diseases, which currently account for a considerable proportion of morbidity in Western society. Further, one human disease, termed "Syndrome X" or "Metabolic Syndrome", is manifested by defective glucose metabolism (insulin resistance), elevated blood pressure (hypertension), and a blood lipid imbalance (dyslipidemia). *See e.g.* Reaven, 1993, *Annu. Rev. Med.* 44:121-131.

The evidence linking elevated serum cholesterol to coronary heart disease is overwhelming. Circulating cholesterol is carried by plasma lipoproteins, which are particles of complex lipid and protein composition that transport lipids in the blood. Low density lipoprotein (LDL) and high density lipoprotein (HDL) are the major cholesterol-carrier proteins. LDL is believed to be responsible for the delivery of cholesterol from the liver, where it is synthesized or obtained from dietary sources, to extrahepatic tissues in the body. The term "reverse cholesterol transport" describes the transport of cholesterol from extrahepatic tissues to the liver, where it is catabolized and eliminated. It is believed that plasma HDL particles play a major role in the reverse transport process, acting as scavengers of tissue cholesterol. HDL is also responsible for the removal of non-cholesterol lipid, oxidized cholesterol and other oxidized products from the bloodstream.

Atherosclerosis, for example, is a slowly progressive disease characterized by the accumulation of cholesterol within the arterial wall. Compelling evidence supports the

belief that lipids deposited in atherosclerotic lesions are derived primarily from plasma apolipoprotein B (apo B)-containing lipoproteins, which include chylomicrons, CLDL, IDL and LDL. The apo B-containing lipoprotein, and in particular LDL, has popularly become known as the "bad" cholesterol. In contrast, HDL serum levels correlate inversely with coronary heart disease. Indeed, high serum levels of HDL are regarded as a negative risk factor. It is hypothesized that high levels of plasma HDL are not only protective against coronary artery disease, but may actually induce regression of atherosclerotic plaque (*e.g.*, see Badimon *et al.*, 1992, *Circulation* 86:(Suppl. III)86-94; Dansky and Fisher, 1999, *Circulation* 100:1762-3.). Thus, HDL has popularly become known as the "good" cholesterol.

2.1. Cholesterol Transport

The fat-transport system can be divided into two pathways: an exogenous one for cholesterol and triglycerides absorbed from the intestine and an endogenous one for cholesterol and triglycerides entering the bloodstream from the liver and other non-hepatic tissue.

In the exogenous pathway, dietary fats are packaged into lipoprotein particles called chylomicrons, which enter the bloodstream and deliver their triglycerides to adipose tissue for storage and to muscle for oxidation to supply energy. The remnant of the chylomicron, which contains cholesteryl esters, is removed from the circulation by a specific receptor found only on liver cells. This cholesterol then becomes available again for cellular metabolism or for recycling to extrahepatic tissues as plasma lipoproteins.

In the endogenous pathway, the liver secretes a large, very-low-density lipoprotein particle (VLDL) into the bloodstream. The core of VLDL consists mostly of triglycerides synthesized in the liver, with a smaller amount of cholesteryl esters either synthesized in the liver or recycled from chylomicrons. Two predominant proteins are displayed on the surface of VLDL, apolipoprotein B-100 (apo B-100) and apolipoprotein E (apo E), although other apolipoproteins are present, such as apolipoprotein CIII (apo CIII) and apolipoprotein CII (apo CII). When a VLDL reaches the capillaries of adipose tissue or of muscle, its triglyceride is extracted. This results in the formation of a new kind of particle called intermediate-density lipoprotein (IDL) or VLDL remnant, decreased in size and enriched in cholesteryl esters relative to a VLDL, but retaining its two apoproteins.

In human beings, about half of the IDL particles are removed from the circulation quickly, generally within two to six hours of their formation. This is because IDL particles bind tightly to liver cells, which extract IDL cholesterol to make new VLDL and bile acids.

The IDL not taken up by the liver is catabolized by the hepatic lipase, an enzyme bound to the proteoglycan on liver cells. Apo E dissociates from IDL as it is transformed to LDL. Apo B-100 is the sole protein of LDL.

Primarily, the liver takes up and degrades circulating cholesterol to bile acids, which are the end products of cholesterol metabolism. The uptake of cholesterol-containing particles is mediated by LDL receptors, which are present in high concentrations on hepatocytes. The LDL receptor binds both apo E and apo B-100 and is responsible for binding and removing both IDL and LDL from the circulation. In addition, remnant receptors are responsible for clearing chylomicrons and VLDL remnants (*i.e.*, IDL). However, the affinity of apo E for the LDL receptor is greater than that of apo B-100. As a result, the LDL particles have a much longer circulating life span than IDL particles; LDL circulates for an average of two and a half days before binding to the LDL receptors in the liver and other tissues. High serum levels of LDL, the "bad" cholesterol, are positively associated with coronary heart disease. For example, in atherosclerosis, cholesterol derived from circulating LDL accumulates in the walls of arteries. This accumulation forms bulky plaques that inhibit the flow of blood until a clot eventually forms, obstructing an artery and causing a heart attack or stroke.

Ultimately, the amount of intracellular cholesterol liberated from the LDL controls cellular cholesterol metabolism. The accumulation of cellular cholesterol derived from VLDL and LDL controls three processes. First, it reduces the cell's ability to make its own cholesterol by turning off the synthesis of HMGCoA reductase, a key enzyme in the cholesterol biosynthetic pathway. Second, the incoming LDL-derived cholesterol promotes storage of cholesterol by the action of cholesterol acyltransferase ("ACAT"), the cellular enzyme that converts cholesterol into cholesteryl esters that are deposited in storage droplets. Third, the accumulation of cholesterol within the cell drives a feedback mechanism that inhibits cellular synthesis of new LDL receptors. Cells, therefore, adjust their complement of LDL receptors so that enough cholesterol is brought in to meet their metabolic needs, without overloading (for a review, see Brown & Goldstein, In, The Pharmacological Basis Of Therapeutics, 8th Ed., Goodman & Gilman, Pergamon Press, New York, 1990, Ch. 36, pp. 874-896).

High levels of apo B-containing lipoproteins can be trapped in the subendothelial space of an artery and undergo oxidation. The oxidized lipoprotein is recognized by scavenger receptors on macrophages. Binding of oxidized lipoprotein to the scavenger receptors can enrich the macrophages with cholesterol and cholesteryl esters independently of the LDL receptor. Macrophages can also produce cholesteryl esters by the action of

ACAT. LDL can also be complexed to a high molecular weight glycoprotein called apolipoprotein(a), also known as apo(a), through a disulfide bridge. The LDL-apo(a) complex is known as Lipoprotein(a) or Lp(a). Elevated levels of Lp(a) are detrimental, having been associated with atherosclerosis, coronary heart disease, myocardial infarction, stroke, cerebral infarction, and restenosis following angioplasty.

2.2. Reverse Cholesterol Transport

Peripheral (non-hepatic) cells predominantly obtain their cholesterol from a combination of local synthesis and uptake of preformed sterol from VLDL and LDL. Cells expressing scavenger receptors, such as macrophages and smooth muscle cells, can also obtain cholesterol from oxidized apo B-containing lipoproteins. In contrast, reverse cholesterol transport (RCT) is the pathway by which peripheral cell cholesterol can be returned to the liver for recycling to extrahepatic tissues, hepatic storage, or excretion into the intestine in bile. The RCT pathway represents the only means of eliminating cholesterol from most extrahepatic tissues and is crucial to maintenance of the structure and function of most cells in the body.

The enzyme in blood involved in the RCT pathway, lecithin:cholesterol acyltransferase (LCAT), converts cell-derived cholesterol to cholesteryl esters, which are sequestered in HDL destined for removal. LCAT is produced mainly in the liver and circulates in plasma associated with the HDL fraction. Cholesterol ester transfer protein (CETP) and another lipid transfer protein, phospholipid transfer protein (PLTP), contribute to further remodeling the circulating HDL population (see for example Bruce *et al.*, 1998, *Annu. Rev. Nutr.* 18:297-330). PLTP supplies lecithin to HDL, and CETP can move cholesteryl ester made by LCAT to other lipoproteins, particularly apoB-containing lipoproteins, such as VLDL. HDL triglyceride can be catabolized by the extracellular hepatic triglyceride lipase, and lipoprotein cholesterol is removed by the liver via several mechanisms.

Each HDL particle contains at least one molecule, and usually two to four molecules, of apolipoprotein (apo A-I). Apo A-I is synthesized by the liver and small intestine as preproapolipoprotein which is secreted as a proprotein that is rapidly cleaved to generate a mature polypeptide having 243 amino acid residues. Apo A-I consists mainly of a 22 amino acid repeating segment, spaced with helix-breaking proline residues. Apo A-I forms three types of stable structures with lipids: small, lipid-poor complexes referred to as pre-beta-1 HDL; flattened discoidal particles, referred to as pre-beta-2 HDL, which contain only polar lipids (*e.g.*, phospholipid and cholesterol); and spherical particles containing both

polar and nonpolar lipids, referred to as spherical or mature HDL (HDL_3 and HDL_2). Most HDL in the circulating population contains both apo A-I and apo A-II, a second major HDL protein. This apo A-I- and apo A-II-containing fraction is referred to herein as the AI/AII-HDL fraction of HDL. But the fraction of HDL containing only apo A-I, referred to herein as the AI-HDL fraction, appears to be more effective in RCT. Certain epidemiologic studies support the hypothesis that the AI-HDL fraction is antiartherogenic (Parra *et al.*, 1992, *Arterioscler. Thromb.* 12:701-707; Decossin *et al.*, 1997, *Eur. J. Clin. Invest.* 27:299-307).

Although the mechanism for cholesterol transfer from the cell surface is unknown, it is believed that the lipid-poor complex, pre-beta-1 HDL, is the preferred acceptor for cholesterol transferred from peripheral tissue involved in RCT. Cholesterol newly transferred to pre-beta-1 HDL from the cell surface rapidly appears in the discoidal pre-beta-2 HDL. PLTP may increase the rate of disc formation (Lagrost *et al.*, 1996, *J. Biol. Chem.* 271:19058-19065), but data indicating a role for PLTP in RCT is lacking. LCAT reacts preferentially with discoidal and spherical HDL, transferring the 2-acyl group of lecithin or phosphatidylethanolamine to the free hydroxyl residue of fatty alcohols, particularly cholesterol, to generate cholesteryl esters (retained in the HDL) and lysolecithin. The LCAT reaction requires an apolipoprotein such apo A-I or apo A-IV as an activator. ApoA-I is one of the natural cofactors for LCAT. The conversion of cholesterol to its HDL-sequestered ester prevents re-entry of cholesterol into the cell, resulting in the ultimate removal of cellular cholesterol. Cholesteryl esters in the mature HDL particles of the AI-HDL fraction are removed by the liver and processed into bile more effectively than those derived from the AI/AII-HDL fraction. This may be due, in part, to the more effective binding of AI-HDL to the hepatocyte membrane. Several HDL receptors have been identified, the most well characterized of which is the scavenger receptor class B, type I (SR-BI) (Acton *et al.*, 1996, *Science* 271:518-520). The SR-BI is expressed most abundantly in steroidogenic tissues (*e.g.*, the adrenals), and in the liver (Landshulz *et al.*, 1996, *J. Clin. Invest.* 98:984-995; Rigotti *et al.*, 1996, *J. Biol. Chem.* 271:33545-33549). Other proposed HDL receptors include HB1 and HB2 (Hidaka and Fidge, 1992, *Biochem J.* 15:161-7; Kurata *et al.*, 1998, *J. Atherosclerosis and Thrombosis* 4:112-7).

While there is a consensus that CETP is involved in the metabolism of VLDL- and LDL-derived lipids, its role in RCT remains controversial. However, changes in CETP activity or its acceptors, VLDL and LDL, play a role in "remodeling" the HDL population. For example, in the absence of CETP, the HDL becomes enlarged particles that are poorly removed from the circulation (for reviews on RCT and HDL, *See* Fielding & Fielding,

1995, *J. Lipid Res.* 36:211-228; Barrans *et al.*, 1996, *Biochem. Biophys. Acta.* 1300:73-85; Hirano *et al.*, 1997, *Arterioscler. Thromb. Vasc. Biol.* 17:1053-1059).

2.3. Reverse Transport of Other Lipids

HDL is not only involved in the reverse transport of cholesterol, but also plays a role in the reverse transport of other lipids, *i.e.*, the transport of lipids from cells, organs, and tissues to the liver for catabolism and excretion. Such lipids include sphingomyelin, oxidized lipids, and lysophophatidylcholine. For example, Robins and Fasulo (1997, *J. Clin. Invest.* 99:380-384) have shown that HDL stimulates the transport of plant sterol by the liver into bile secretions.

2.4. Peroxisome Proliferator Activated Receptor Pathway

Peroxisome proliferators are a structurally diverse group of compounds that, when administered to rodents, elicit dramatic increases in the size and number of hepatic and renal peroxisomes, as well as concomitant increases in the capacity of peroxisomes to metabolize fatty acids via increased expression of the enzymes required for the β-oxidation cycle (Lazarow and Fujiki, 1985, *Ann. Rev. Cell Biol.* 1:489-530; Vamecq and Draye, 1989, *Essays Biochem.* 24:1115-225; and Nelali *et al.*, 1988, *Cancer Res.* 48:5316-5324). Chemicals included in this group are the fibrate class of hypolipidemic drugs, herbicides, and phthalate plasticizers (Reddy and Lalwani, 1983, *Crit. Rev. Toxicol.* 12:1-58). Peroxisome proliferation can also be elicited by dietary or physiological factors, such as a high-fat diet and cold acclimatization.

Insight into the mechanism whereby peroxisome proliferators exert their pleiotropic effects was provided by the identification of a member of the nuclear hormone receptor superfamily activated by these chemicals (Isseman and Green, 1990, *Nature* 347:645-650). This receptor, termed peroxisome proliferator activated receptor α ($PPAR_\alpha$), was subsequently shown to be activated by a variety of medium and long-chain fatty acids. $PPAR_\alpha$ activates transcription by binding to DNA sequence elements, termed peroxisome proliferator response elements (PPRE), in the form of a heterodimer with the retinoid X receptor (RXR). RXR is activated by 9-cis retinoic acid (*see* Kliewer *et al.*, 1992, *Nature* 358:771-774; Gearing *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90:1440-1444, Keller *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90:2160-2164; Heyman *et al.*, 1992, *Cell* 68:397-406, and Levin *et al.*, 1992, *Nature* 355:359-361). Since the discovery of $PPAR_\alpha$, additional

isoforms of PPAR have been identified, *e.g.*, $PPAR_{\beta}$, $PPAR_{\gamma}$ and $PPAR_{\delta}$, which have similar functions and are similarly regulated.

PPREs have been identified in the enhancers of a number of gene-encoding proteins that regulate lipid metabolism. These proteins include the three enzymes required for peroxisomal β-oxidation of fatty acids; apolipoprotein A-I; medium-chain acyl-CoA dehydrogenase, a key enzyme in mitochondrial β-oxidation; and aP2, a lipid binding protein expressed exclusively in adipocytes (reviewed in Keller and Whali, 1993, *TEM,* 4:291-296; *see also* Staels and Auwerx, 1998, *Atherosclerosis* 137 Suppl:S19-23). The nature of the PPAR target genes coupled with the activation of PPARs by fatty acids and hypolipidemic drugs suggests a physiological role for the PPARs in lipid homeostasis.

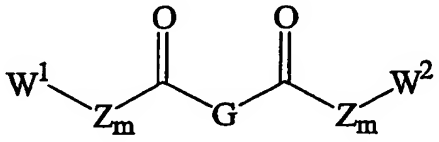
2.5. Current Cholesterol Management Therapies

None of the commercially available cholesterol management drugs has a general utility in regulating lipid, lipoprotein, insulin and glucose levels in the blood. Thus, compounds that have one or more of these utilities are clearly needed. Further, there is a clear need to develop safer drugs that are efficacious at lowering serum cholesterol, increasing HDL serum levels, preventing coronary heart disease, and/or treating existing disease such as atherosclerosis, obesity, diabetes, and other diseases that are affected by lipid metabolism and/or lipid levels. There is also a clear need to develop drugs that may be used with other lipid-altering treatment regimens in a synergistic manner. There is still a further need to provide useful therapeutic agents whose solubility and Hydrophile/Lipophile Balance (HLB) can be readily varied.

Citation or identification of any reference in Section 2 of this application is not an admission that such reference is available as prior art to the present invention.

3. Summary of The Invention

In one embodiment, the invention relates to a compound of formula **I**:



I

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, stereoisomer, diastereomer, racemate, geometric isomer or mixtures thereof wherein:

(a) each occurrence of Z is independently CH_2, CH=CH, or phenyl, wherein each occurrence of m is independently an integer ranging from 1 to 9, but when Z is phenyl then its associated m is 1;

(b) G is $(CH_2)_x$, $CH_2CH=CHCH_2$, CH=CH, CH_2–phenyl–CH_2, or phenyl, wherein x is 2, 3, or 4;

(c) W^1 and W^2 are independently L, V, $C(R^1)(R^2)$–$(CH_2)_c$–$C(R^3)(R^4)$–$(CH_2)_n$–Y, or $C(R^1)(R^2)$–$(CH_2)_c$–V, wherein c is 1 or 2 and n is an independent integer ranging from 0 to 4;

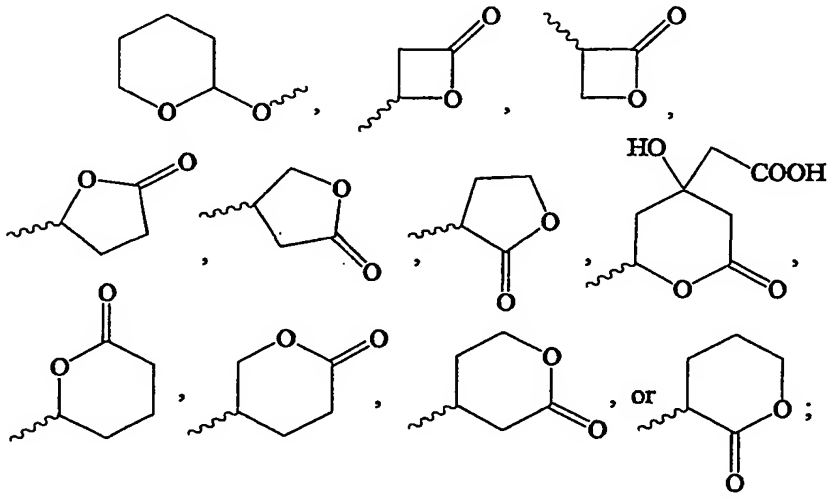
(d) each occurrence of R^1 and R^2 is independently $(C_1$–$C_6)$alkyl, $(C_2$–$C_6)$alkenyl, $(C_2$–$C_6)$alkynyl, phenyl, or benzyl or when W^1 or W^2 is $C(R^1)(R^2)$–$(CH_2)_c$–$C(R^3)(R^4)$–Y, then R^1 and R^2 can both be H;

(e) R^3 is H, $(C_1$–$C_6)$alkyl, $(C_2$–$C_6)$alkenyl, $(C_2$–$C_6)$alkynyl, $(C_1$–$C_6)$alkoxy, phenyl, benzyl, Cl, Br, CN, NO_2, or CF_3;

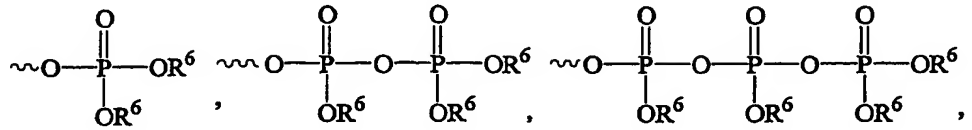
(f) R^4 is OH, $(C_1$–$C_6)$alkyl, $(C_2$–$C_6)$alkenyl, $(C_2$–$C_6)$alkynyl, $(C_1$–$C_6)$alkoxy, phenyl, benzyl, Cl, Br, CN, NO_2, or CF_3;

(g) L is $C(R^1)(R^2)$–$(CH_2)_n$–Y; where n is an independent integer ranging from 0 to 4;

(h) V is



(i) each occurrence of Y is independently OH, COOH, CHO, $COOR^5$, SO_3H,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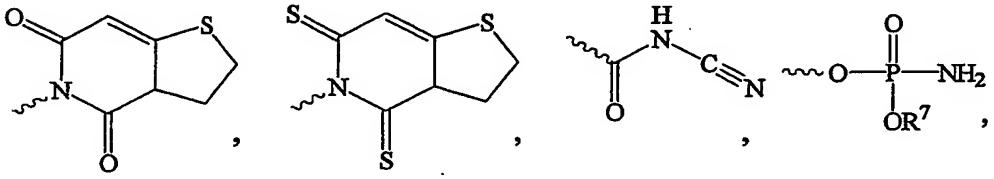
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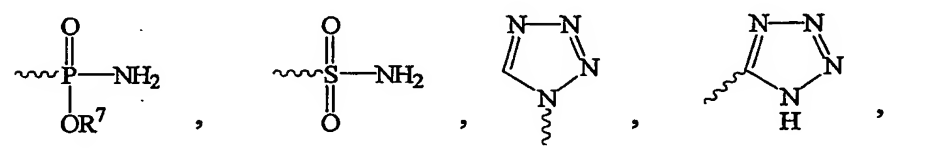
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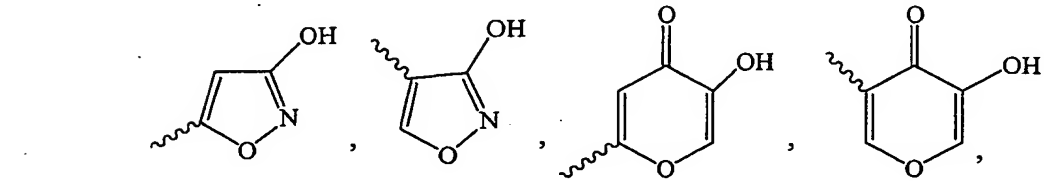
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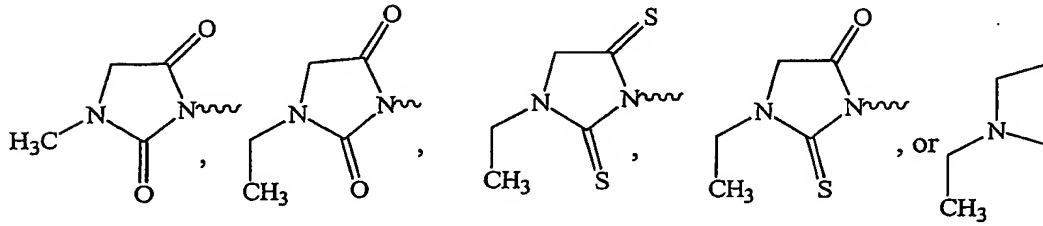
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where:

(i) R^5 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, $(C_1–C_6)$alkoxy, or phenyl groups,

(ii) each occurrence of R^6 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl and is unsubstituted or substituted with one or two halo, OH, $C_1–C_6$ alkoxy, or phenyl groups; and

(iii) each occurrence of R^7 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl;

provided that:

(i) if G is $(CH_2)_x$, x is 4, each occurrence of Z is CH_2, each occurrence of m is 4, and W^1 is $-CH(CH_3)CO_2H$, then W^2 is not the same as W^1;

(ii) if G is CH_2-phenyl-CH_2, each occurrence of Z is CH_2, each occurrence of m is 2, and W^1 is $-C(CH_3)_2CH(CO_2CH_2CH_3)_2$, then W^2 is not the same as W^1;

(iii) if G is CH_2-phenyl-CH_2, each occurrence of Z is CH_2, each occurrence of m is 2, and W^1 is $-C(CH_3)_2CH_2(CO_2CH_2CH_3)$, then W^2 is not the same as W^1;

(iv) if G is CH_2-phenyl-CH_2, each occurrence of Z is CH_2, each occurrence of m is 1, and W^1 is $-COCH_2C(CH_3)_2CH_2CO_2H$, then W^2 is not the same as W^1;

(v) if G is $(CH_2)_x$, x is 4, each occurrence of Z is CH_2, each occurrence of m is 2, and W^1 is $-C(phenyl)_2CH_2CO_2H$, then W^2 is not the same as W^1;

(vi) if G is CH=CH, each occurrence of Z is CH_2, each occurrence of m is 1, and W^1 is $-C(CH_3)_2CH_2(CO_2H)$, then W^2 is not the same as W^1; and

(vii) if G is phenyl, each occurrence of Z is CH_2, each occurrence of m is 1, and W^1 is $-C(phenyl)_2CO_2H$, then W^2 is not the same as W^1.

Preferred compounds of formula I are those wherein:

(a) W^1 and W^2 are independently L, V, or $C(R^1)(R^2)–(CH_2)_c–V$, where c is 1 or 2; and

(b) R^1 and R^2 are independently $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl.

Other preferred compounds of formula **I** are those wherein W^1 is L.

Other preferred compounds of formula **I** are those wherein W^1 is V.

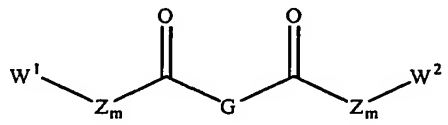
Other preferred compounds of formula **I** are those wherein W^1 is $C(R^1)(R^2)–(CH_2)_c–C(R^3)(R^4)–(CH_2)_n–Y$.

Other preferred compounds of formula **I** are those wherein W^1 is $C(R^1)(R^2)–(CH_2)_c–V$.

Other preferred compounds of formula **I** are those wherein W^1 and W^2 are independent L groups.

Other preferred compounds of formula **I** are those wherein each occurrence of Y is independently OH, $COOR^5$, or COOH.

In another embodiment, the invention relates to a compound of the formula **Ia**:



Ia

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, stereoisomer, geometric isomer or mixtures thereof wherein:

(a) each occurrence of Z is independently CH_2 or CH=CH, wherein each occurrence of m is independently an integer ranging from 1 to 9;

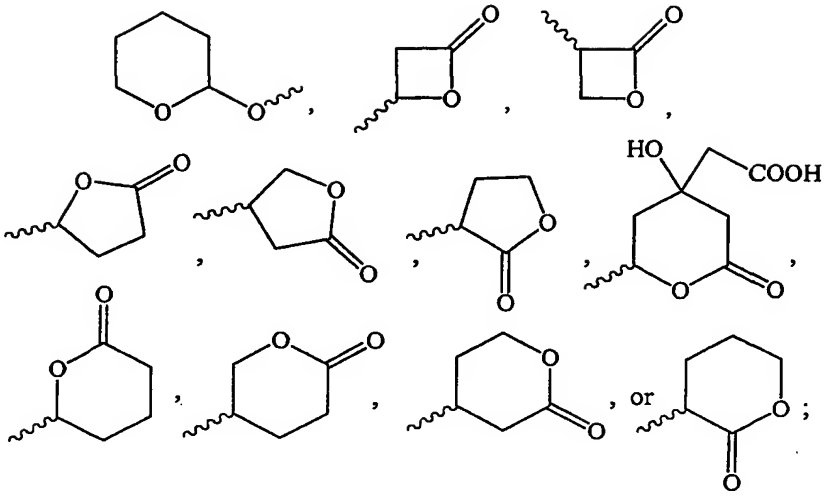
(b) G is $(CH_2)_x$, $CH_2CH=CHCH_2$, or CH=CH, where x is 2, 3, or 4;

(c) W^1 and W^2 are independently L, V, or $C(R^1)(R^2)–(CH_2)_c–V$, where c is 1 or 2;

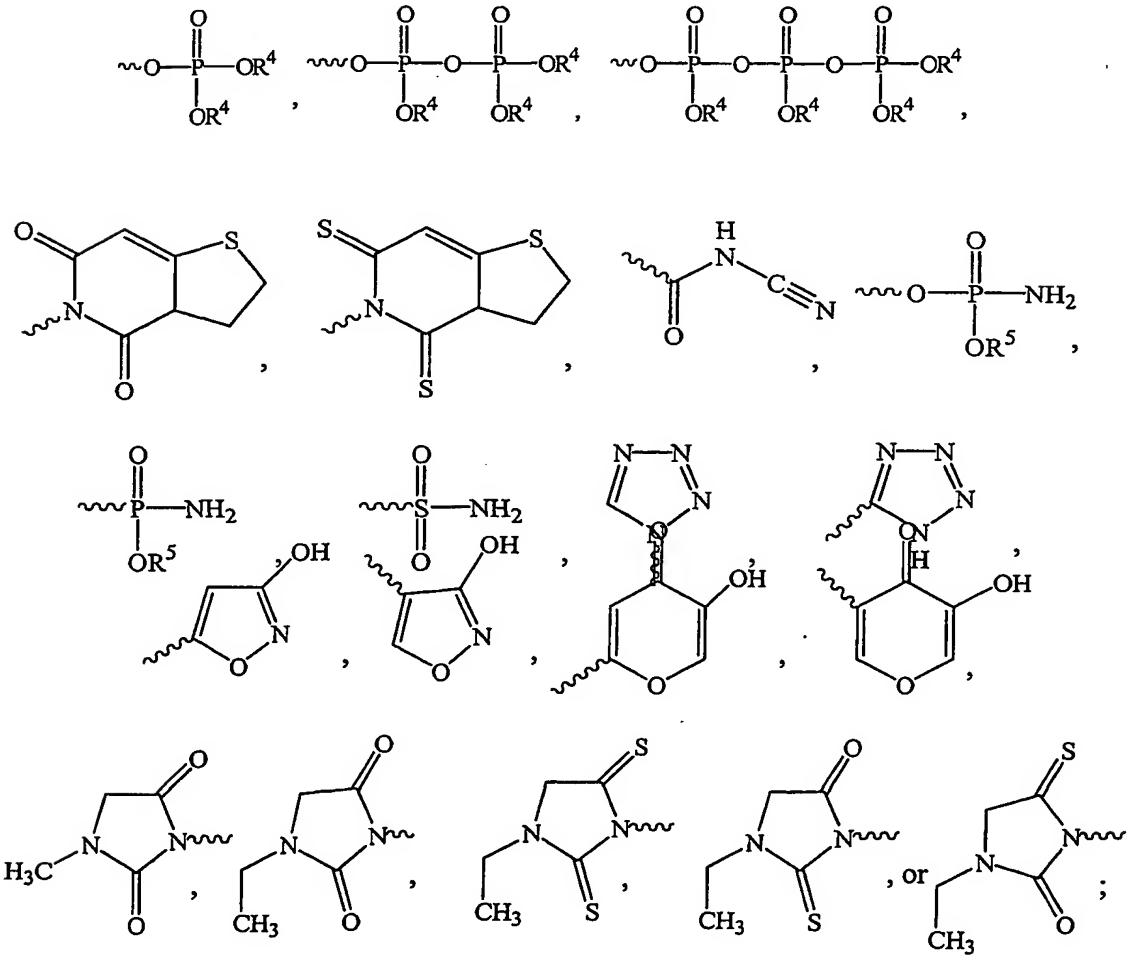
(d) each occurrence of R^1 and R^2 is independently $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl;

(e) L is $C(R^1)(R^2)–(CH_2)_n–Y$, where n is an independent integer ranging from 0 to 4;

(f) V is



(g) each occurrence of Y is independently OH, COOH, CHO, $(CH_2)_nCOOR^3$, SO_3H,



where:

(i) R^3 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, $(C_1–C_6)$alkoxy, or phenyl groups,

(ii) each occurrence of R^4 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl and is unsubstituted or substituted with one or two halo, OH, $C_1–C_6$ alkoxy, or phenyl groups; and

(iii) each occurrence of R^5 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl;

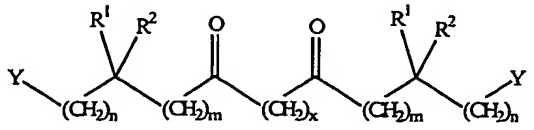
provided that:

(i) if x is 4, each occurrence of Z is CH_2, each occurrence of m is 4, and W^1 is $-CH(CH_3)CO_2H$, then W^2 is not the same as W^1; and

(ii) if x is 4, each occurrence of Z is CH_2, each occurrence of m is 2, and W^1 is $-C(phenyl)_2CH_2CO_2H$, then W^2 is not the same as W^1.

Preferably, in formula **Ia** each occurrence of Y is independently OH, $COOR^3$, or COOH.

In yet another embodiment, the invention relates to a compound of the formula **Ib**:



Ib

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, stereoisomer, geometric isomer or mixtures thereof wherein:

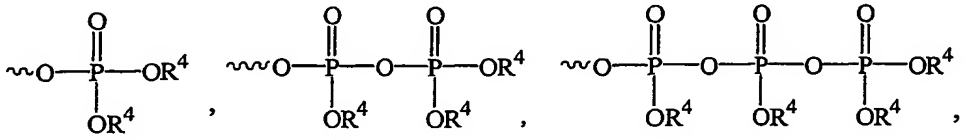
(a) each occurrence of m is independently an integer ranging from 1 to 9;

(b) x is 2, 3, or 4;

(c) each occurrence of n is an independent integer ranging from 0 to 4;

(d) each occurrence of R^1 and R^2 is independently $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl; and

(e) each occurrence of Y is independently OH, COOH, CHO, $COOR^3$, SO_3H,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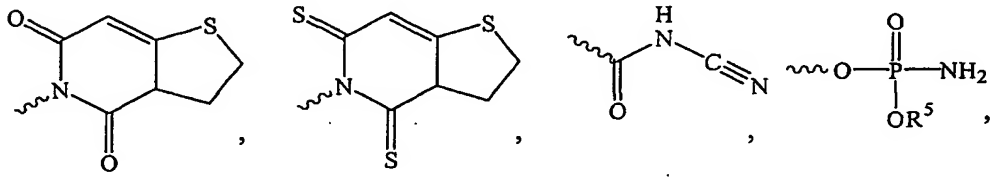
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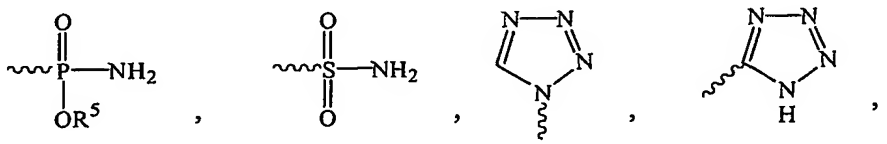
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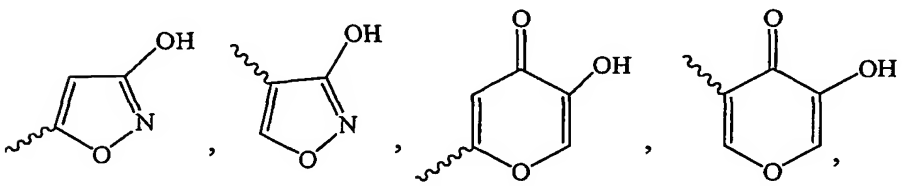
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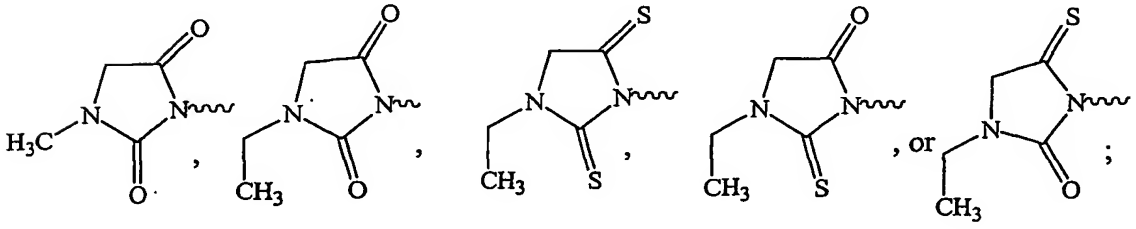

, or ;

where:

(i) R^3 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, $(C_1–C_6)$alkoxy, or phenyl groups,

(ii) each occurrence of R^4 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl and is unsubstituted or substituted with one or two halo, OH, $C_1–C_6$ alkoxy, or phenyl groups; and

(iii) each occurrence of R^5 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl;

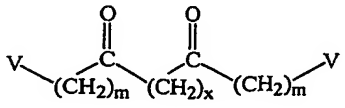
provided that:

(i) if x is 4 each occurrence of m is 4, and W^1 is $-CH(CH_3)CO_2H$, then W^2 is not the same as W^1; and

(ii) if x is 4 occurrence of m is 2, and W^1 is $-C(phenyl)_2CH_2CO_2H$, then W^2 is not the same as W^1.

Preferably in formula **Ib**, each occurrence of Y is independently OH, $COOR^3$, or COOH.

In still another embodiment, the invention relates to a compound of the formula **Ic**:



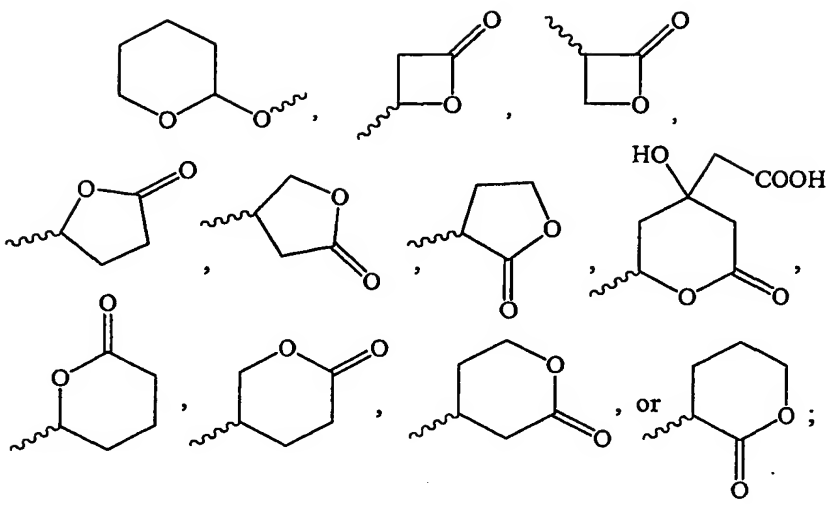
Ic

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, stereoisomer, geometric isomer or mixtures thereof wherein:

(a) each occurrence of m is an independent integer ranging from 1 to 9;

(b) x is 2, 3, or 4;

(c) V is

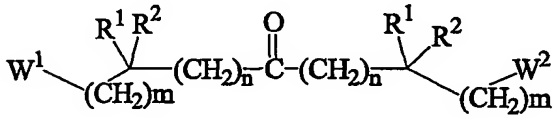


provided that:

(i) if x is 4 each occurrence of m is 4, and W^1 is $-CH(CH_3)CO_2H$, then W^2 is not the same as W^1; and

(ii) if x is 4 each occurrence of m is 2, and W^1 is $-C(phenyl)_2CH_2CO_2H$, then W^2 is not the same as W^1.

In another embodiment, the invention relates to a compound of the formula **II**:



II

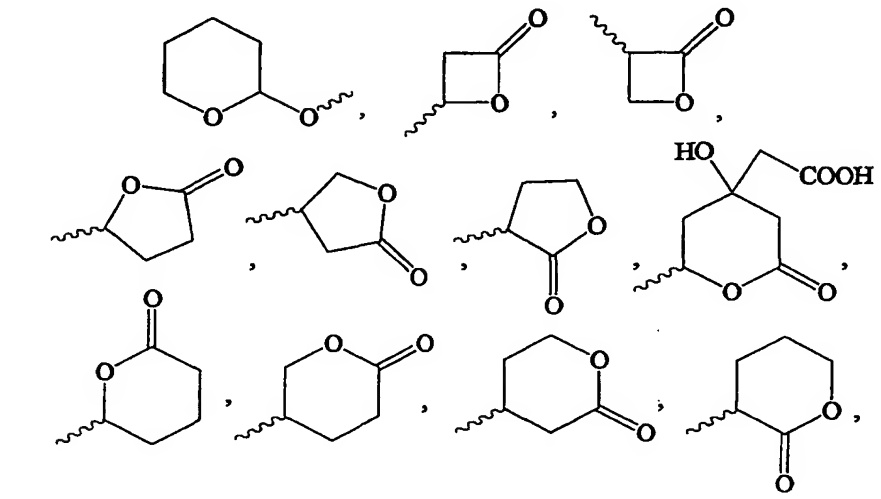
or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, stereoisomer, geometric isomer or mixtures thereof wherein:

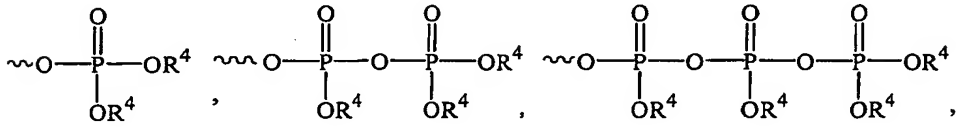
(a) R^1 and R^2 are independently $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl; or R^1, R^2, and the carbon to which they are both attached are taken together to form a $(C_3–C_7)$cycloalkyl group;

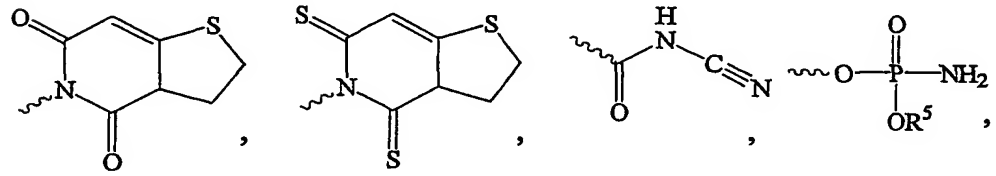
(b) n is an integer ranging from 1 to 5;

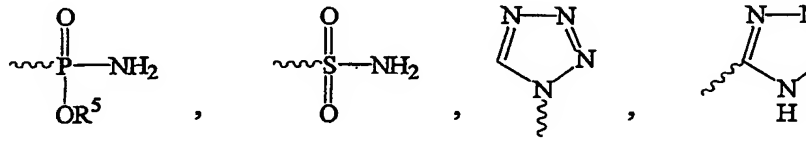
(c) each occurrence of m is independently an integer ranging from 0 to 4;

(d) each occurrence of W^1 and W^2 is independently CH_2OH, COOH, CHO, $OC(O)R^3$, $C(O)OR^3$, SO_3H,









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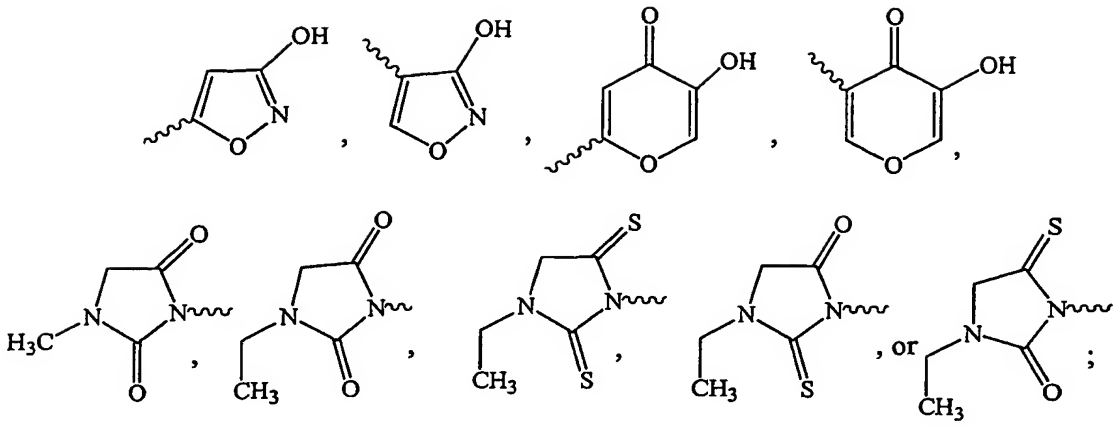


where:

(i) R^3 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, $(C_1–C_6)$alkoxy, or phenyl groups,

(ii) each occurrence of R^4 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl and is unsubstituted or substituted with one or two halo, OH, $C_1–C_6$ alkoxy, or phenyl groups;

(iii) each occurrence of R^5 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl; and

(iv) each occurrence of n is independently an integer ranging from 0 to 4.

Preferred compounds of formula **II** are those wherein each occurrence of W is independently OH, $COOR^3$, or COOH.

Other preferred compounds of formula **II** are those wherein R^1 and R^2 are independent $(C_1–C_6)$alkyl groups.

Other preferred compounds of formula **II** are those wherein m is 0.

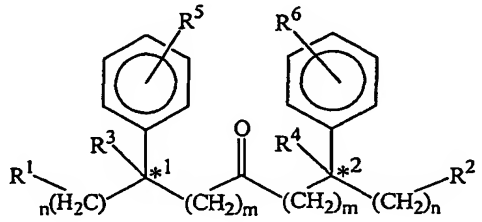
Other preferred compounds of formula **II** are those wherein m is 1.

Other preferred compounds of formula **II** are those wherein R^1 and R^2 are each independently $(C_1–C_6)$ alkyl.

Other preferred compounds of formula **II** are those wherein R^1 and R^2 are each methyl.

Other preferred compounds of formula **II** are those wherein W^1 and/or W^2 is COOH or CH_2OH.

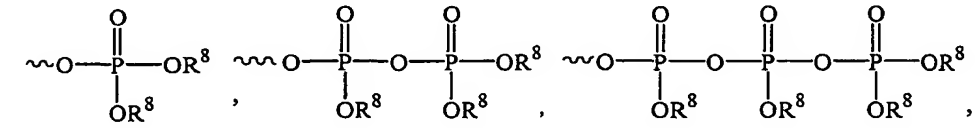
In another embodiment, the invention relates to a compound of the formula **IIa**:

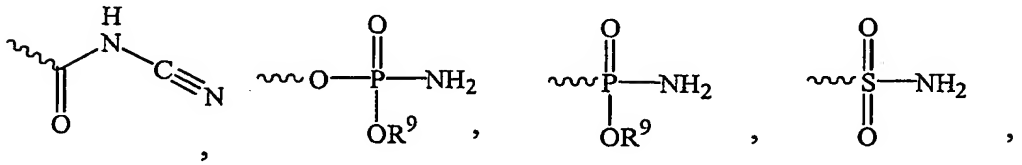


IIa

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, stereoisomer, geometric isomer or mixtures thereof wherein:

(a) R^1 and R^2 are OH, COOH, CHO, $COOR^7$, SO_3H,





where:

(i) R^7 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, $(C_1–C_6)$alkoxy, or phenyl groups,

(ii) each occurrence of R^8 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl and is unsubstituted or substituted with one or two halo, OH, $C_1–C_6$ alkoxy, or phenyl groups, and

(iii) each occurrence of R^9 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl;

(b) R^3 and R^4 are $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl;

(c) R^5 and R^6 are hydrogen, halogen, $(C_1–C_4)$alkyl, $(C_1–C_4)$alkoxy, (C_6)aryloxy, CN, or NO_2, $N(R^5)_2$ where R^5 is H, $(C_1–C_4)$ alkyl, phenyl, or benzyl;

(d) each occurrence of m is independently an integer ranging from 1 to 5;

(e) each occurrence of n is independently an integer ranging from 0 to 4; and

(f) C^{*1} and C^{*2} represent independent chiral-carbon centers, wherein each center may independently be R or S.

Preferred compounds of formula **IIa** are those wherein each occurrence of R^1 and R^2 is independently OH, $COOR^7$, or COOH.

Other preferred compounds of formula **IIa** are those wherein m is 0.

Other preferred compounds of formula **IIa** are those wherein m is 1.

Other preferred compounds of formula **IIa** are those wherein R^1 and/or R^2 is COOH or CH_2OH.

Other preferred compounds of formula **IIa** are those wherein R^3 and R^4 are each independently $(C_1–C_6)$ alkyl.

Other preferred compounds of formula **IIa** are those wherein R^3 and R^4 are each methyl.

Other preferred compounds of formula **IIa** are those wherein C^{*1} is of the stereochemical configuration R or substantially R.

Other preferred compounds of formula **IIa** are those wherein C^{*1} is of the stereochemical configuration S or substantially S.

Other preferred compounds of formula **IIa** are those wherein C^{*2} is of the stereochemical configuration R or substantially R.

Other preferred compounds of formula **IIa** are those wherein C^{*2} is of the stereochemical configuration S or substantially S.

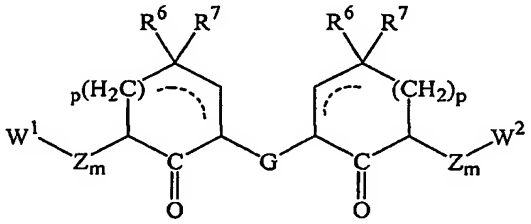
In a particular embodiment, compounds of formula **IIa** are those wherein C^{*1} C^{*2} are of the stereochemical configuration (S^1,S^2) or substantially (S^1,S^2).

In another particular embodiment, compounds of formula **IIa** are those wherein C^{*1} C^{*2} are of the stereochemical configuration (S^1,R^2) or substantially (S^1,R^2).

In another particular embodiment, compounds of formula **IIa** are those wherein C^{*1} C^{*2} are of the stereochemical configuration (R^1,R^2) or substantially (R^1,R^2).

In another particular embodiment, compounds of formula **IIa** are those wherein C^{*1} C^{*2} are of the stereochemical configuration (R^1,S^2) or substantially (R^1,S^2).

In still another embodiment, the invention relates to a compound of the formula **III**:



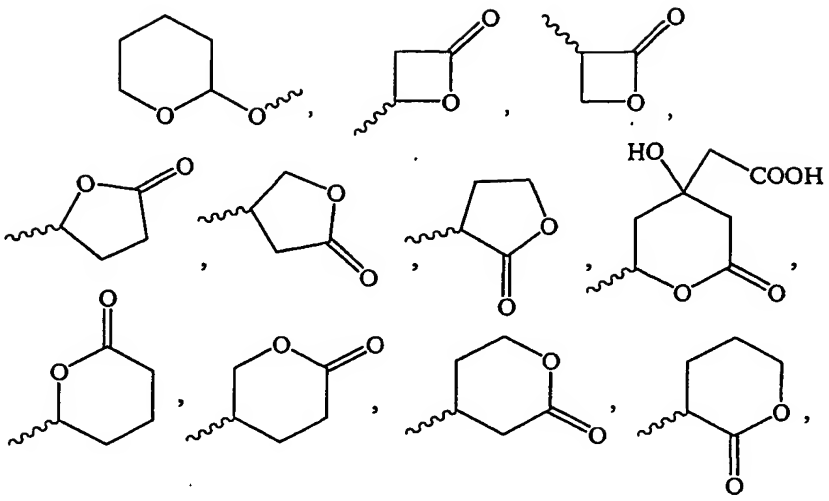
III

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, stereoisomer, geometric isomer or mixtures thereof wherein:

(a) each occurrence of Z is independently CH_2, CH=CH, or phenyl, where each occurrence of m is independently an integer ranging from 1 to 5, but when Z is phenyl then its associated m is 1;

(b) G is $(CH_2)_x$, $CH_2CH{=}CHCH_2$, CH=CH, CH_2–phenyl–CH_2, or phenyl, where x is an integer ranging from 1 to 4;

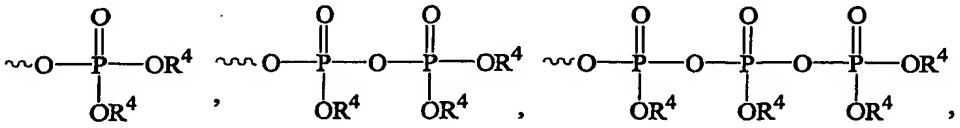
(c) W^1 and W^2 are independently $C(R^1)(R^2)$–$(CH_2)_n$–Y where n is an integer ranging from 0 to 4;

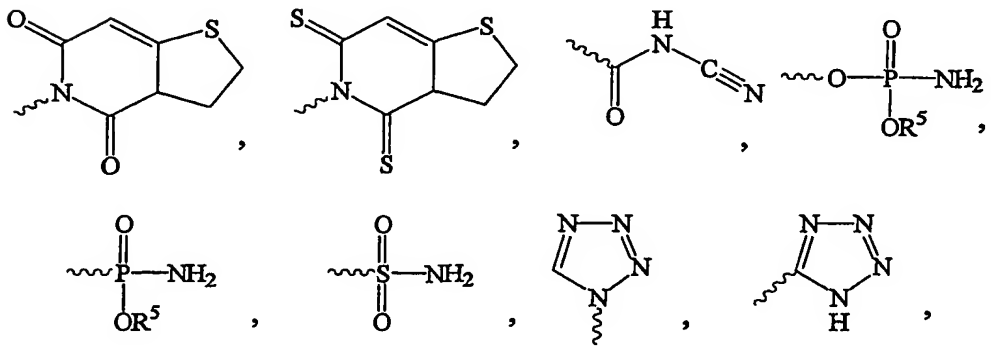


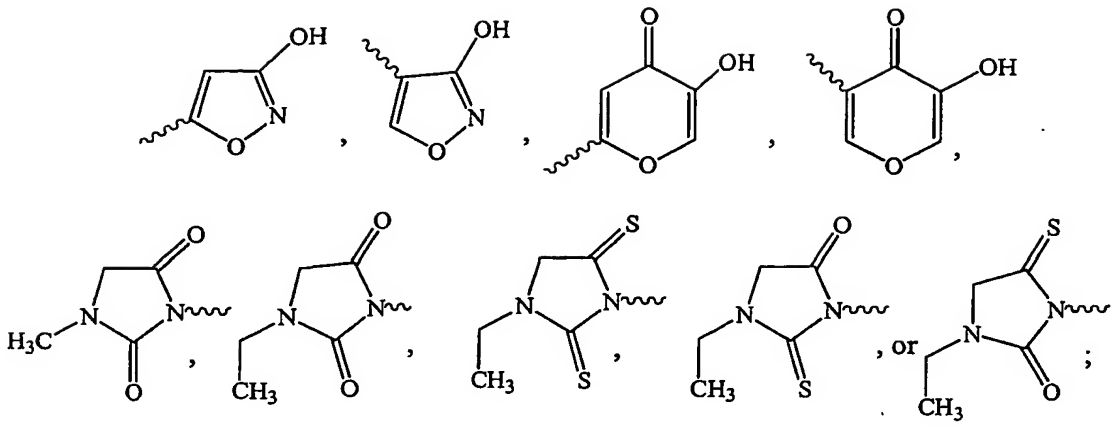
(d) each occurrence of R^1 and R^2 is independently $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl, or where R^1 and R^2 are both hydrogen;

(e) each occurrence of R^6 and R^7 is independently H, (C_1-C_6)alkyl, or where R^6 and R^7 are taken together to form a carbonyl group;

(f) each occurrence of Y is independently OH, COOH, CHO, $COOR^3$, SO_3H,







where:

(i) R^3 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, $(C_1–C_6)$alkoxy, or phenyl groups,

(ii) each occurrence of R^4 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl and is unsubstituted or substituted with one or two halo, OH, $(C_1–C_6)$ alkoxy, or phenyl groups,

(iii) each occurrence of R^5 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl; and

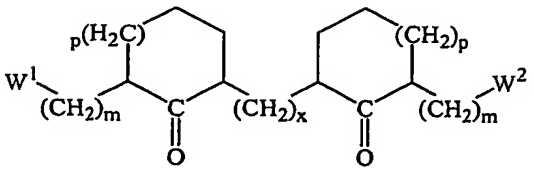
(g) each occurrence of p is independently 0 or 1, where the broken line represents an optional presence of one or more additional carbon-carbon bonds that when present complete one or more carbon-carbon double bonds.

Preferred compounds of formula **III** are those wherein each occurrence of Y is independently OH, $COOR^3$, or COOH.

Other preferred compounds of formula **III** are those wherein p is 2.

Other preferred compounds of formula **III** are those wherein p is 3.

In yet another embodiment, the invention relates to a compound of the formula **IIIa**:



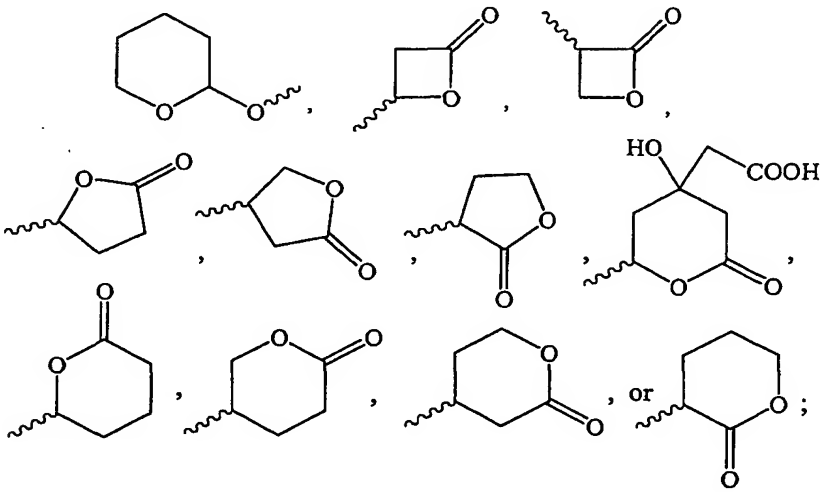
IIIa

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, stereoisomer, geometric isomer or mixtures thereof wherein:

(a) each occurrence of m is independently an integer ranging from 1 to 5;

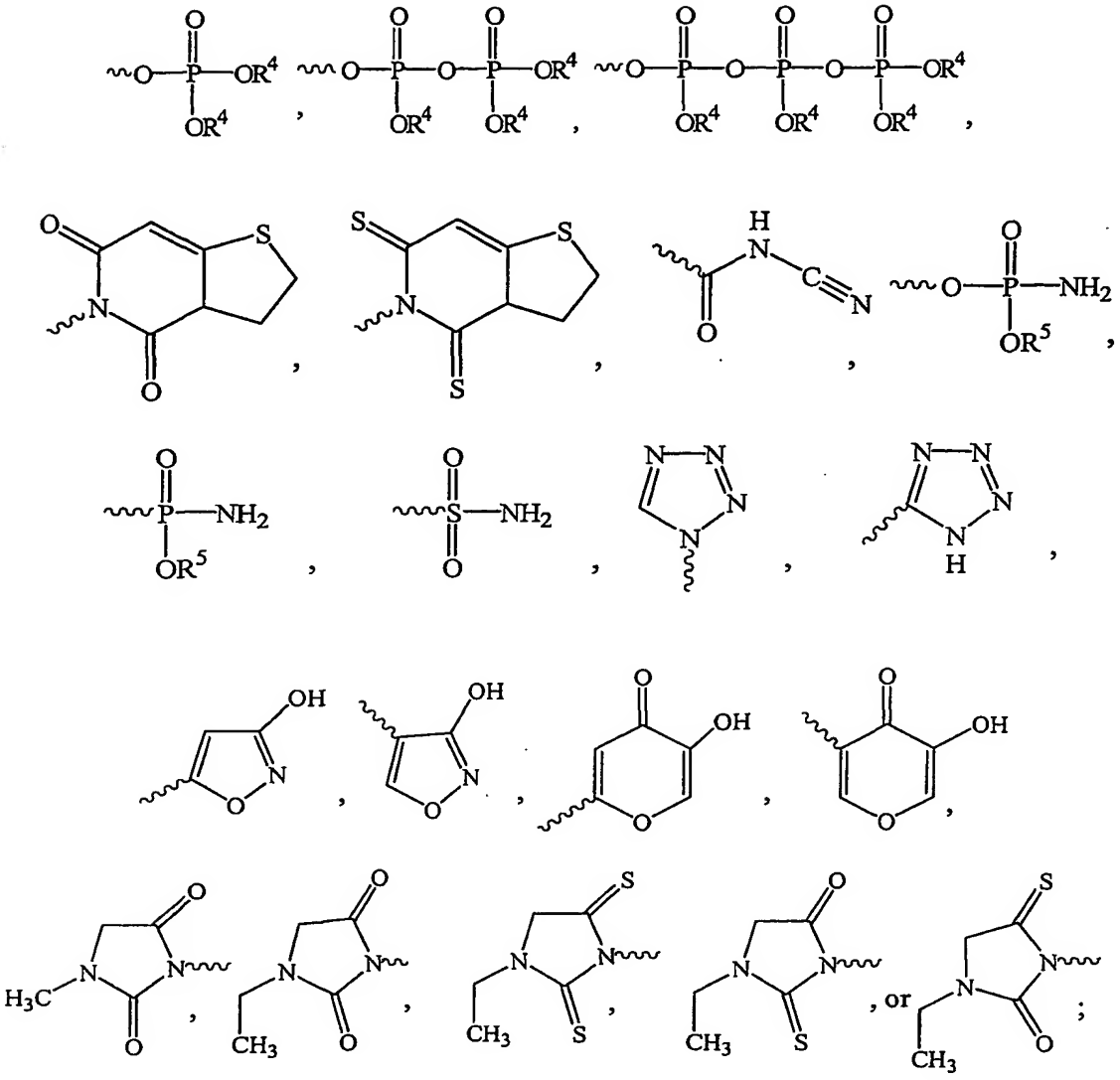
(b) x is an integer ranging from 1 to 4;

(c) W^1 and W^2 are independently $C(R^1)(R^2)$–$(CH_2)_n$–Y; where n is an integer ranging from 0 to 4,



(d) each occurrence of R^1 or R^2 is independently $(C_1$–$C_6)$alkyl, $(C_2$–$C_6)$alkenyl, $(C_2$–$C_6)$alkynyl, phenyl, or benzyl;

(e) each occurrence of Y is independently OH, COOH, CHO, $COOR^3$, SO_3H,



where:

(i) R^3 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, $(C_1–C_6)$alkoxy, or phenyl groups,

(ii) each occurrence of R^4 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl and is unsubstituted or substituted with one or two halo, OH, $C_1–C_6$ alkoxy, or phenyl groups,

(iii) each occurrence of R^5 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl; and

(f) each occurrence of p is independently 0 or 1.

Preferably in compound **IIIa**, W^1 and W^2 are independent $C(R^1)(R^2)$–Y groups and each occurrence of Y is independently OH, $COOR^3$, or COOH.

The compounds of the invention are useful in medical applications for treating or preventing cardiovascular diseases, dyslipidemias, dyslipoproteinemias, disorders of glucose metabolism, Alzheimer's Disease, Syndrome X, PPAR-associated disorders, septicemia, thrombotic disorders, obesity, pancreatitis, hypertension, renal diseases, cancer, inflammation, and impotence. As used herein, the phrase "compounds of the invention" means, collectively, the compounds of formulas **I, II,** and **III** and pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates, or mixures of stereoisomers thereof. Compounds of formula **I** encompass subgroup formulas **Ia, Ib, and Ic**. Compounds of formula **II** encompass subgroup formula **IIa** and compounds of formula **III** encompass subgroup of formula **IIIa**. Thus, "compound of the invention" collectively means compound of formulas **I, Ia, Ib, Ic, II, IIa, III,** and **IIIa** and pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates, or mixures of stereoisomers thereof. The compounds of the invention are identified herein by their chemical structure and/or chemical name. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound's identity.

3.1. Brief Description of the Drawings

Various aspects of the invention can be understood with reference to the figures described below:

FIG. 1 illustrates the effect of one week of daily oral gavage treatment on lipoprotein total cholesterol in chow-fed male Sprague-Dawley rats;

FIG. 2 illustrates the effect of one week of daily oral gavage treatment on serum lipids in chow-fed male Sprague-Dawley rats;

FIG. 3 illustrates the effect of two weeks of daily oral gavage treatment on lipoprotein total cholesterol in chow-fed obese female Zucker rats;

FIG. 4 is a table illustrating the effect of two weeks of daily oral gavage treatment using a specific compound of the invention in chow-fed obese female Zucker rats; and

FIG. 5 is a table illustrating the effect of two weeks of daily oral gavage treatment using a specific compound of the invention on the synthesis of saponfied and non-saponified

lipids in hepatocyte cells isolated from male Sprague-Dawley rats.

4. Detailed Description of the Invention

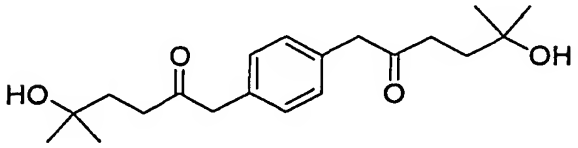
The present invention provides novel compounds useful for treating or preventing a cardiovascular disease, dyslipidemia, dyslipoproteinemia, a disorder of glucose metabolism, Alzheimer's Disease, Syndrome X, a PPAR-associated disorder, septicemia, a thrombotic disorder, obesity, pancreatitis, hypertension, a renal disease, cancer, inflammation, and impotence.

In this regard, the compounds of the invention are particularly useful when incorporated in a pharmaceutical composition having a carrier, excipient, diluent, or a mixture thereof. A composition of the invention need not contain additional ingredients, such as an excipient, other than a compound of the invention. Accordingly, in one embodiment, the compositions of the invention can omit pharmaceutically acceptable excipients and diluents and can be delivered in a gel cap or drug delivery device. Accordingly, the present invention provides methods for treating or preventing cardiovascular diseases, dyslipidemias, dyslipoproteinemias, disorders of glucose metabolism, Alzheimer's Disease, Syndrome X, PPAR-associated disorders, septicemia, thrombotic disorders, obesity, pancreatitis, hypertension, renal diseases, cancer, inflammation, or impotence, comprising administering to a patient in need thereof a therapeutically effective amount of a compound or composition of the invention.

In certain embodiments of the invention, a compound of the invention is administered in combination with another therapeutic agent. The other therapeutic agent provides additive or synergistic value relative to the administration of a compound of the invention alone. The therapeutic agent can be a lovastatin; a thiazolidinedione or fibrate; a bile-acid-binding-resin; a niacin; an anti-obesity drug; a hormone; a tyrophostine; a sulfonylurea-based drug; a biguanide; an α-glucosidase inhibitor; an apolipoprotein A-I agonist; apolipoprotein E; a cardiovascular drug; an HDL-raising drug; an HDL enhancer; or a regulator of the apolipoprotein A-I, apolipoprotein A-IV and/or apolipoprotein genes.

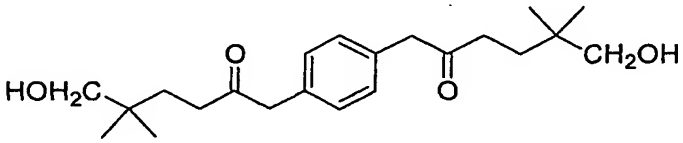
Table 1 lists the compounds of the invention:

TABLE 1: Compounds of the Invention



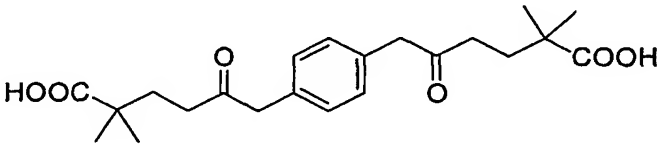
I-1

5-Hydroxy-1-[4-(5-hydroxy-5-methyl-2-oxo-hexyl)-phenyl]-5-methyl-hexan-2-one



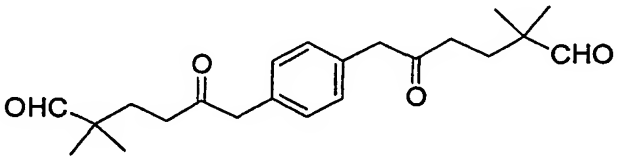
I-2

6-Hydroxy-1-[4-(6-hydroxy-5,5-dimethyl-2-oxo-hexyl)-phenyl]-5,5-dimethyl-hexan-2-one



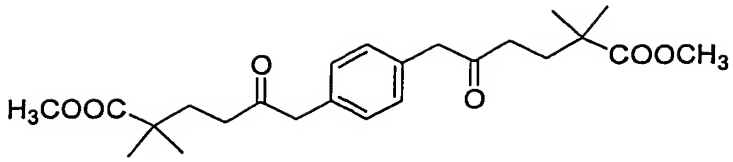
I-3

6-[4-(5-Carboxy-5-methyl-2-oxo-hexyl)-phenyl]-2,2-dimethyl-5-oxo-hexanoic acid



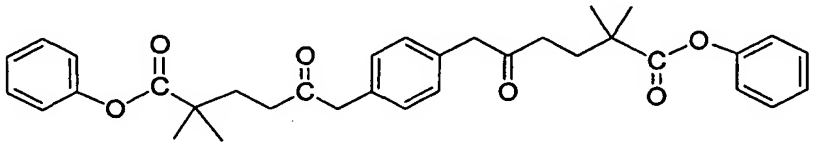
I-4

6-[4-(5,5-Dimethyl-2,6-dioxo-hexyl)-phenyl]-2,2-dimethyl-5-oxo-hexanal



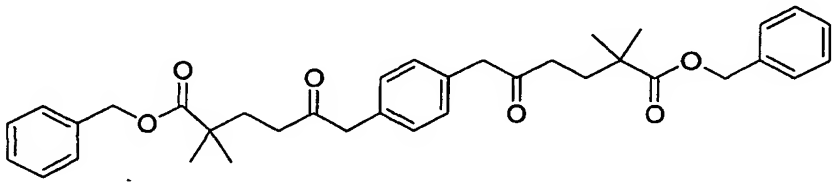
I-5

6-[4-(5-Methoxycarbonyl-5-methyl-2-oxo-hexyl)-phenyl]-2,2-dimethyl-5-oxo-hexanoic acid methyl ester



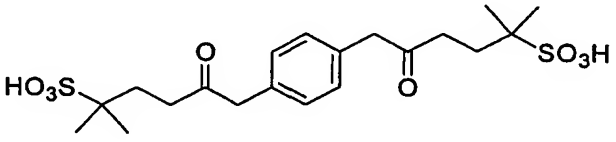
I-6

2,2-Dimethyl-6-[4-(5-methyl-2-oxo-5-phenoxycarbonyl-hexyl)-phenyl]-5-oxo-hexanoic acid phenyl ester



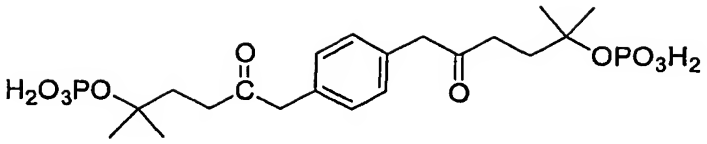
I-7

6-[4-(5-Benzyloxycarbonyl-5-methyl-2-oxo-hexyl)-phenyl]-2,2-dimethyl-5-oxo-hexanoic acid benzyl ester



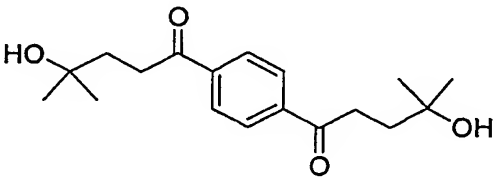
I-8

2-Methyl-6-[4-(5-methyl-2-oxo-5-sulfo-hexyl)-phenyl]-5-oxo-hexane-2-sulfonic acid



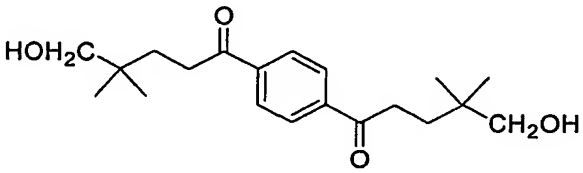
I-9

Phosphoric acid mono-{1,1-dimethyl-5-[4-(5-methyl-2-oxo-5-phosphonooxy-hexyl)-phenyl]-4-oxo-pentyl} ester



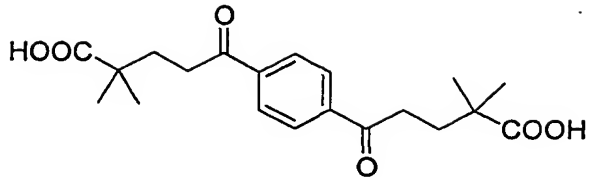
I-10

4-Hydroxy-1-[4-(4-hydroxy-4-methyl-pentanoyl)-phenyl]-4-methyl-pentan-1-one



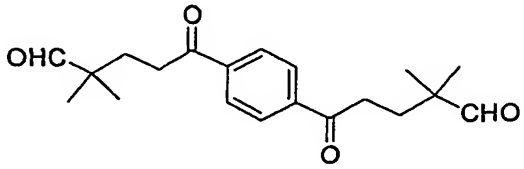
I-11

5-Hydroxy-1-[4-(5-hydroxy-4,4-dimethyl-pentanoyl)-phenyl]-4,4-dimethyl-pentan-1-one



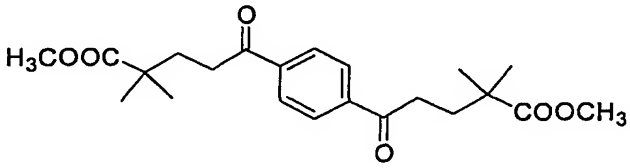
I-12

5-[4-(4-Carboxy-4-methyl-pentanoyl)-phenyl]-2,2-dimethyl-5-oxo-pentanoic acid



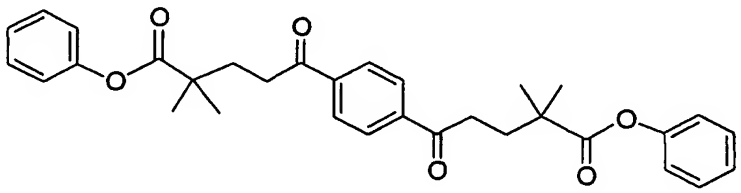
I-13

5-[4-(4,4-Dimethyl-5-oxo-pentanoyl)-phenyl]-2,2-dimethyl-5-oxo-pentanal



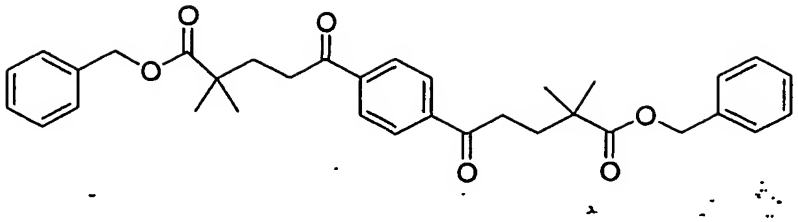
I-14

5-[4-(4-Methoxycarbonyl-4-methyl-pentanoyl)-phenyl]-2,2-dimethyl-5-oxo-pentanoic acid methyl ester



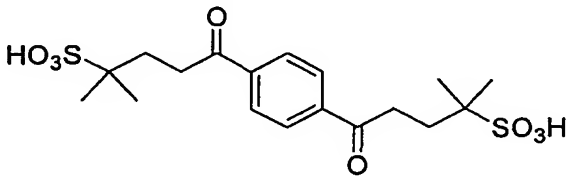
I-15

2,2-Dimethyl-6-[4-(5-methyl-2-oxo-5-phenoxycarbonyl-hexyl)-phenyl]-5-oxo-hexanoic acid phenyl ester



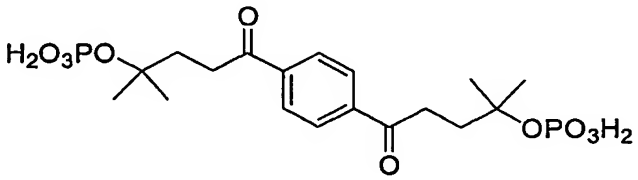
I-16

5-[4-(4-Benzyloxycarbonyl-4-methyl-pentanoyl)-phenyl]-2,2-dimethyl-5-oxo-pentanoic acid benzyl ester



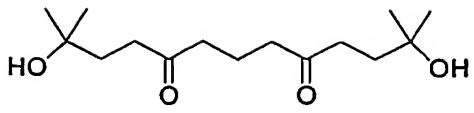
I-17

2-Methyl-5-[4-(4-methyl-4-sulfo-pentanoyl)-phenyl]-5-oxo-pentane-2-sulfonic acid



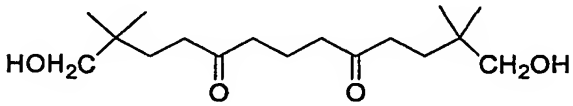
I-18

Phosphoric acid mono-{1,1-dimethyl-4-[4-(4-methyl-4-phosphonooxy-pentanoyl)-phenyl]-4-oxo-butyl} ester



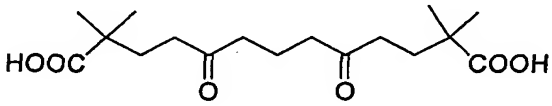
Ib-1

2,12-Dihydroxy-2,12-dimethyl-tridecane-5,9-dione



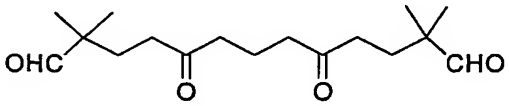
Ib-2

1,13-Dihydroxy-2,2,12,12-tetramethyl-tridecane-5,9-dione



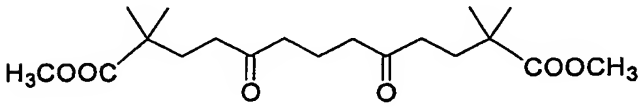
Ib-3

2,2,12,12-Tetramethyl-5,9-dioxo-tridecanedioic acid



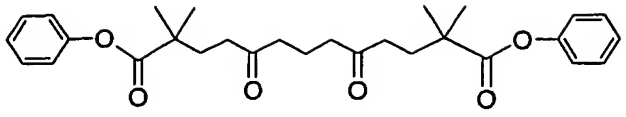
Ib-4

2,2,12,12-Tetramethyl-5,9-dioxo-tridecanedial



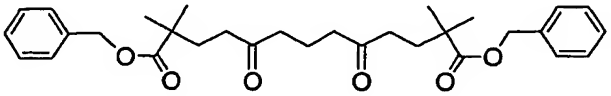
Ib-5

2,2,12,12-Tetramethyl-5,9-dioxo-tridecanedioic acid dimethyl ester



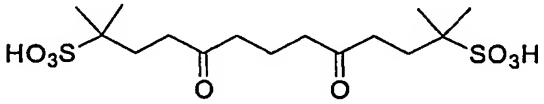
Ib-6

2,2,12,12-Tetramethyl-5,9-dioxo-tridecanedioic acid diphenyl ester



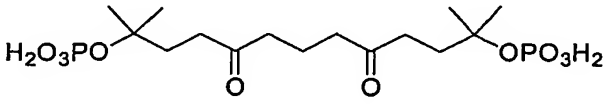
Ib-7

2,2,12,12-Tetramethyl-5,9-dioxo-tridecanedioic acid dibenzyl ester



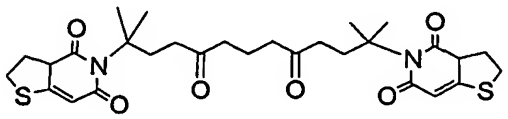
Ib-8

2,12-Dimethyl-5,9-dioxo-tridecane-2,12-disulfonic acid



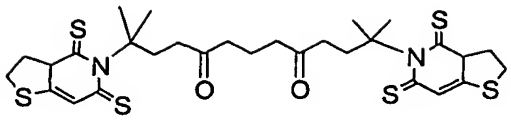
Ib-9

Phosphoric acid mono-(1,1,11-trimethyl-4,8-dioxo-11-phosphonooxy-dodecyl) ester



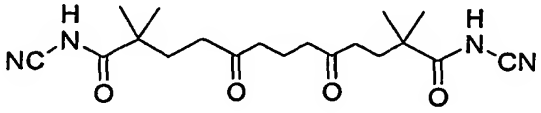
Ib-10

2,12-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,12-dimethyl-tridecane-5,9-dione



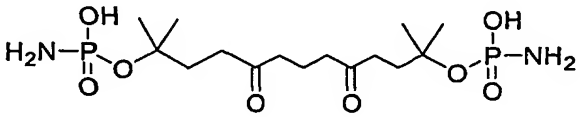
Ib-11

2,12-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,12-dimethyl-tridecane-5,9-dione



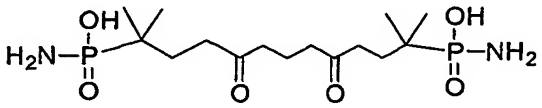
Ib-12

2,2,12,12-Tetramethyl-5,9-dioxo-tridecanedioic acid dicyanimide



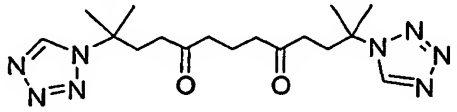
Ib-13

Phosphoramidic acid mono-[11-(amino-hydroxy-phosphoryloxy)-1,1,11-trimethyl-4,8-dioxo-dodecyl] ester



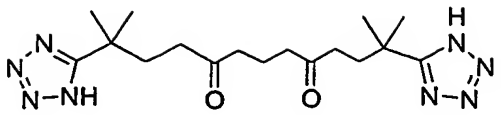
Ib-14

2,12-Dimethyl-2,12-bis-(amino-hydroxy-phosphoryloxy)-tridecane-5,9-dione



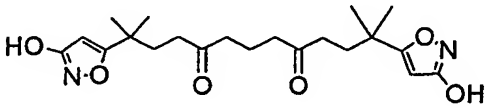
Ib-15

2,12-Dimethyl-2,12-bis-tetrazol-1-yl-tridecane-5,9-dione



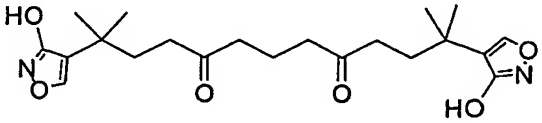
Ib-16

2,12-Dimethyl-2,12-bis-(1H-tetrazol-5-yl)-tridecane-5,9-dione



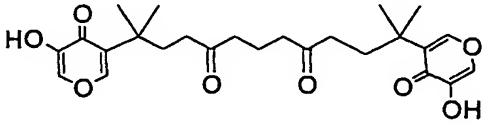
Ib-17

2,12-Bis-(3-hydroxy-isoxazol-5-yl)-2,12-dimethyl-tridecane-5,9-dione



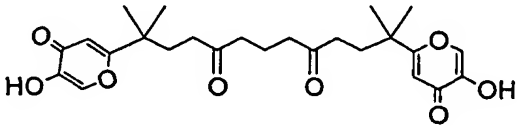
Ib-18

2,12-Bis-(3-hydroxy-isoxazol-4-yl)-2,12-dimethyl-tridecane-5,9-dione



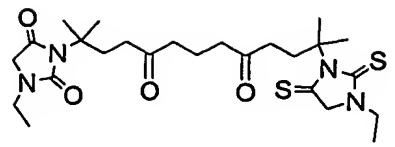
Ib-19

2,12-Bis-(5-hydroxy-4-oxo-4H-pyran-3-yl)-2,12-dimethyl-tridecane-5,9-dione



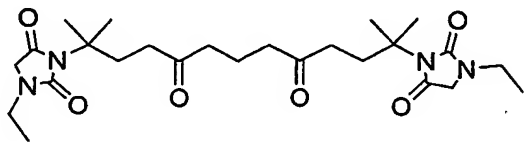
Ib-20

2,12-Bis-(5-hydroxy-4-oxo-4H-pyran-2-yl)-2,12-dimethyl-tridecane-5,9-dione



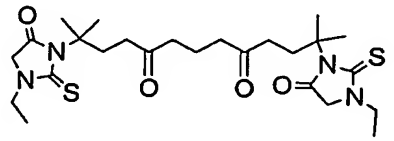
Ib-21

1-Ethyl-3-[11-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-1,1,11-trimethyl-4,8-dioxo-dodecyl]-imidazolidine-2,4-dione



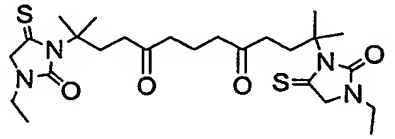
Ib-22

2,12-Bis-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-2,12-dimethyl-tridecane-5,9-dione



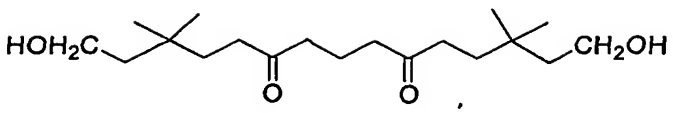
Ib-23

2,12-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-2,12-dimethyl-tridecane-5,9-dione



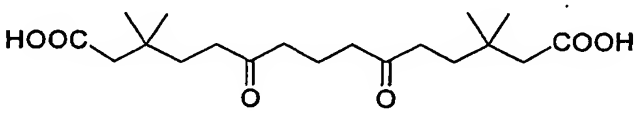
Ib-24

2,12-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-2,12-dimethyl-tridecane-5,9-dione



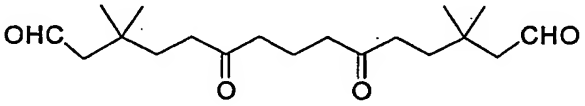
Ib-25

1,15-Dihydroxy-3,3,13,13-tetramethyl-pentadecane-6,10-dione



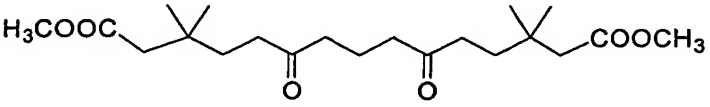
Ib-26

3,3,13,13-Tetramethyl-6,10-dioxo-pentadecanedioic acid



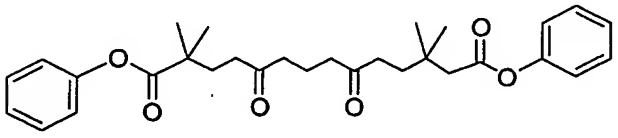
Ib-27

3,3,13,13-Tetramethyl-6,10-dioxo-pentadecanedial



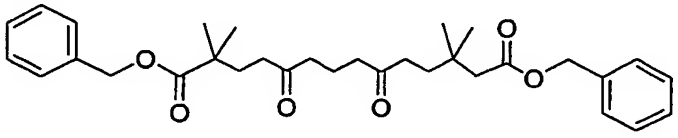
Ib-28

3,3,13,13-Tetramethyl-6,10-dioxo-pentadecanedioic acid dimethyl ester



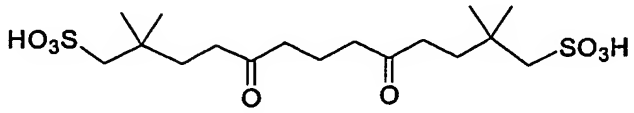
Ib-29

2,2,12,12-Tetramethyl-5,9-dioxo-tetradecanedioic acid diphenyl ester



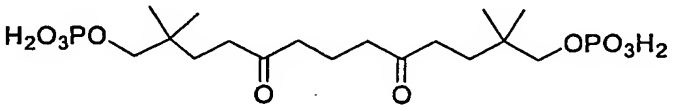
Ib-30

3,3,13,13-Tetramethyl-6,10,14-trioxo-16-phenyl-hexadecanoic acid benzyl ester



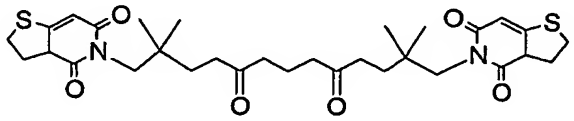
Ib-31

2,2,12,12-Tetramethyl-5,9-dioxo-tridecane-1,13-disulfonic acid



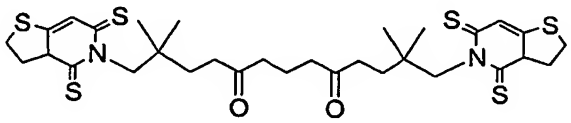
Ib-32

Phosphoric acid mono-(2,2,12,12-tetramethyl-5,9-dioxo-13-phosphonooxy-tridecyl) ester



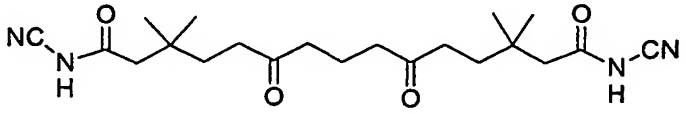
Ib-33

1,13-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione



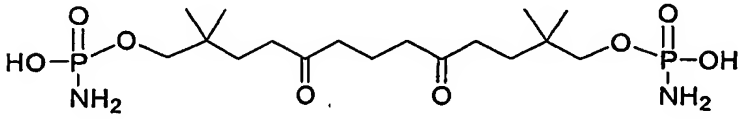
Ib-34

1,13-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione



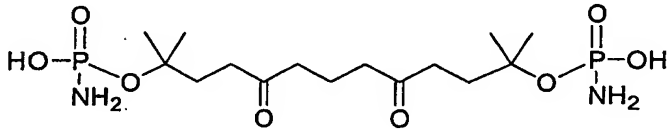
Ib-35

3,3,13,13-Tetramethyl-6,10-dioxo-pentadecanedioic acid dicyanimide



Ib-36

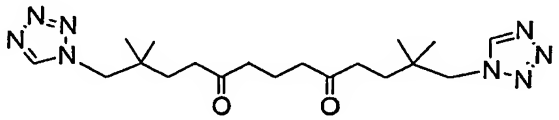
Phosphoramidic acid mono-[13-(amino-hydroxy-phosphoryloxy)-2,2,12,12-tetramethyl-6,9-dioxo-tridecyl] ester



Ib-37

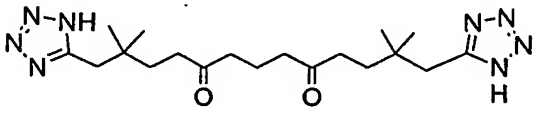
Phosphoramidic acid

mono-[11-(amino-hydroxy-phosphoryloxy)-1,1,11-trimethyl-4,8-dioxo-dodecyl] ester



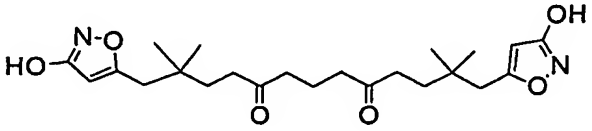
Ib-38

2,2,12,12-Tetramethyl-1,13-bis-tetrazol-1-yl-tridecane-5,9-dione



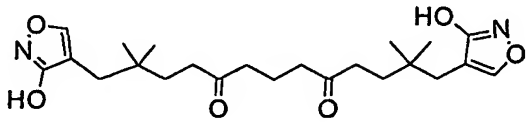
Ib-39

1,13-Bis-(3-hydroxy-isoxazol-5-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione



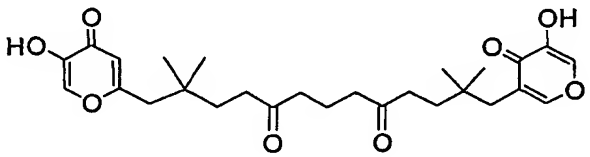
Ib-40

1,13-Bis-(3-hydroxy-isoxazol-5-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione



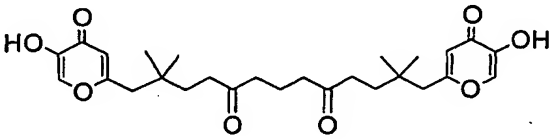
Ib-41

1,13-Bis-(3-hydroxy-isoxazol-4-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione



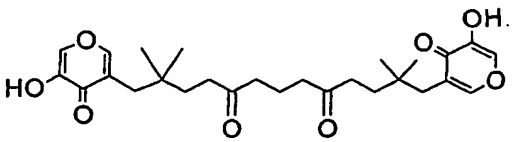
Ib-42

1-(5-Hydroxy-4-oxo-4H-pyran-3-yl)-13-(5-hydroxy-4-oxo-4H-pyran-2-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione



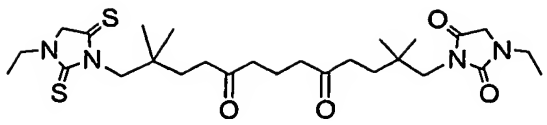
Ib-43

1,13-Bis-(5-hydroxy-4-oxo-4H-pyran-2-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione



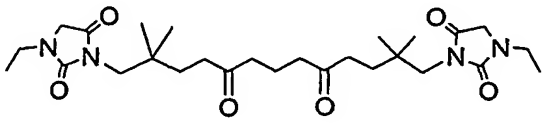
Ib-44

1,13-Bis-(5-hydroxy-4-oxo-4H-pyran-3-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione



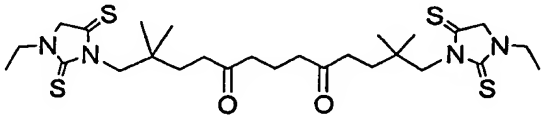
Ib-45

1-Ethyl-3-[13-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-2,2,12,12-tetramethyl-5,9-dioxo-tridecyl]-imidazolidine-2,4-dione



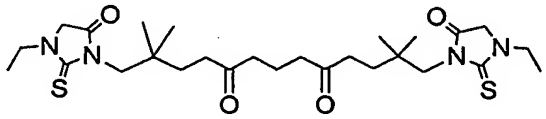
Ib-46

1,13-Bis-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione



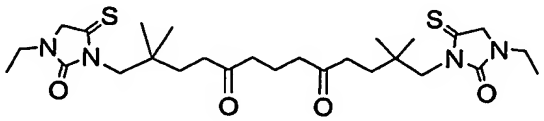
Ib-47

1,13-Bis-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione



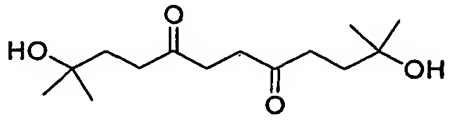
Ib-48

1,13-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione



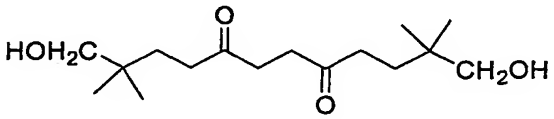
Ib-49

1,13-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione



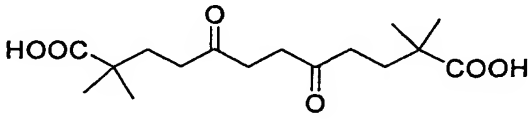
Ib-50

2,11-Dihydroxy-2,11-dimethyl-dodecane-5,8-dione



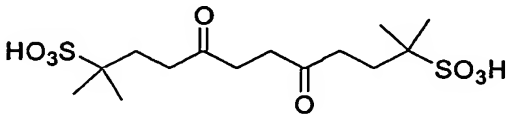
Ib-51

1,12-Dihydroxy-2,2,11,11-tetramethyl-dodecane-5,8-dione



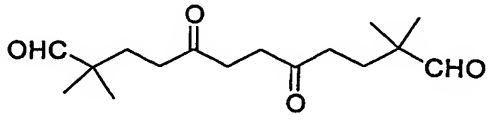
Ib-52

2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid



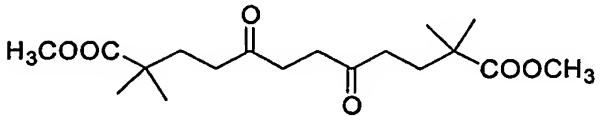
Ib-53

2,11-Dimethyl-5,8-dioxo-dodecane-2,11-disulfonic acid



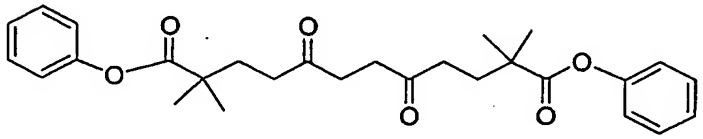
Ib-54

2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedial



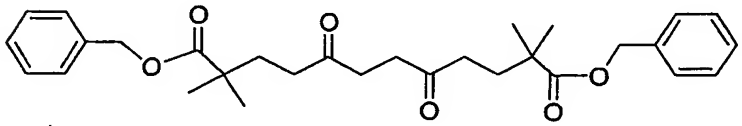
Ib-55

2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid dimethyl ester



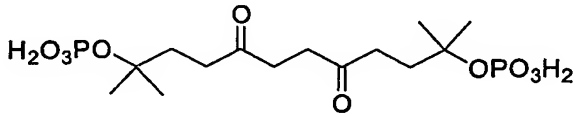
Ib-56

2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid diphenyl ester



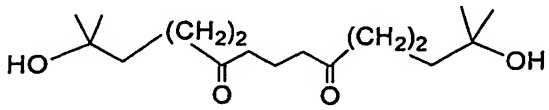
Ib-57

2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid dibenzyl ester



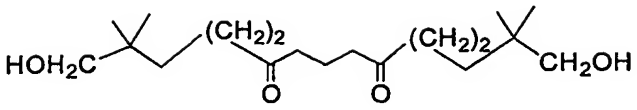
Ib-58

Phosphoric acid mono-(1,1,10-trimethyl-4,7-dioxo-10-phosphonooxy-undecyl) ester



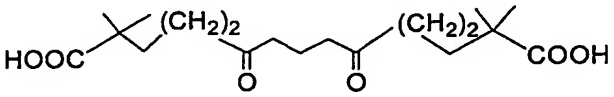
Ib-59

2,14-Dihydroxy-2,14-dimethyl-pentadecane-6,10-dione



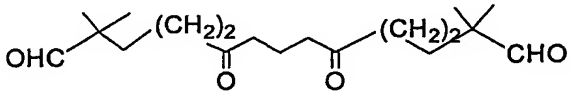
Ib-60

1,15-Dihydroxy-2,2,14,14-tetramethyl-pentadecane-6,10-dione



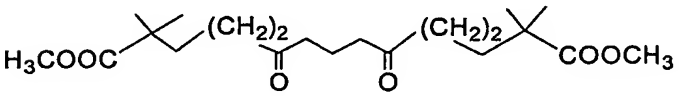
Ib-61

2,2,14,14-Tetramethyl-6,10-dioxo-pentadecanedioic acid



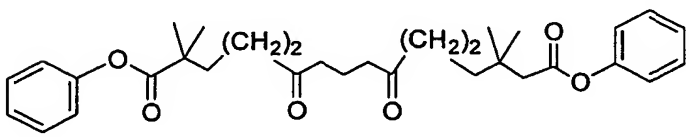
Ib-62

2,2,14,14-Tetramethyl-6,10-dioxo-pentadecanedial



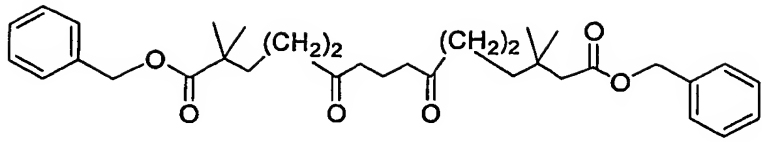
Ib-63

2,2,14,14-Tetramethyl-6,10-dioxo-pentadecanedioic acid dimethyl ester



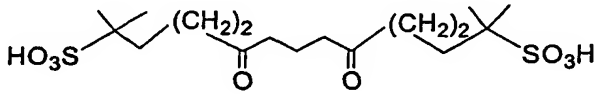
Ib-64

2,2,14,14-Tetramethyl-6,10-dioxo-hexadecanedioic acid diphenyl ester



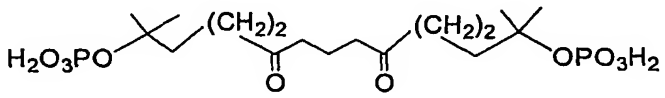
Ib-65

2,2,14,14-Tetramethyl-6,10-dioxo-hexadecanedioic acid dibenzyl ester



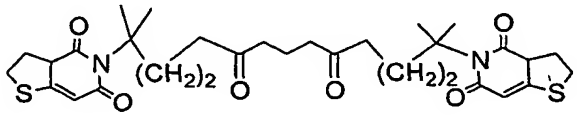
Ib-66

2,14-Dimethyl-6,10-dioxo-pentadecane-2,14-disulfonic acid



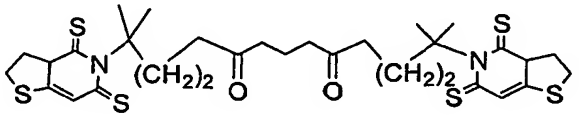
Ib-67

Phosphoric acid mono-(1,1,13-trimethyl-5,9-dioxo-13-phosphonooxy-tetradecyl) ester



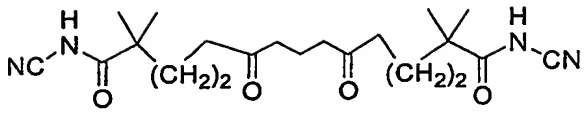
Ib-68

2,14-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,14-dimethyl-pentadecane-6,10-dione



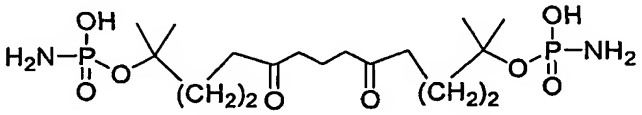
Ib-69

2,14-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,14-dimethyl-pentadecane-6,10-dione



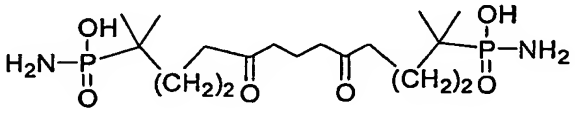
Ib-70

2,2,14,14-Tetramethyl-6,10-dioxo-pentadecanedioic acid dicyanimide



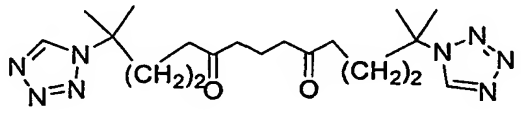
Ib-71

Phosphoramidic acid mono-[13-(amino-hydroxy-phosphoryloxy)-1,1,13-trimethyl-5,9-dioxo-tetradecyl] ester



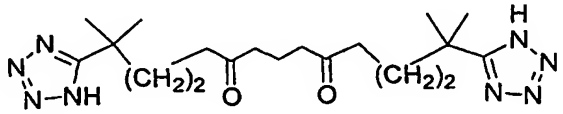
Ib-72

2,14-Dimethyl-2,14-bis-(amino-hydroxy-phosphoryloxy)-pentadecane-6,10-dione



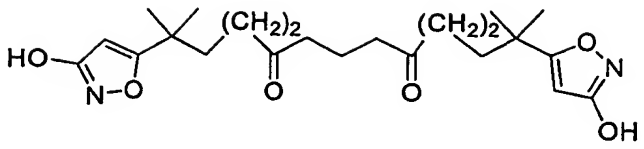
Ib-73

2,14-Dimethyl-2,14-bis-tetrazol-1-yl-pentadecane-6,10-dione



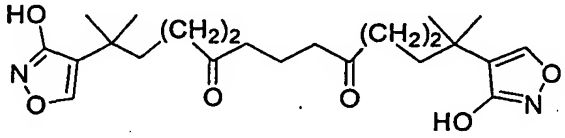
Ib-74

2,14-Dimethyl-2,14-bis-(1H-tetrazol-5-yl)-pentadecane-6,10-dione



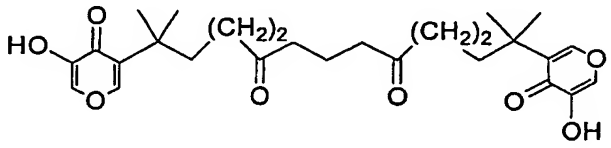
Ib-75

2,14-Bis-(3-hydroxy-isoxazol-5-yl)-2,14-dimethyl-pentadecane-6,10-dione



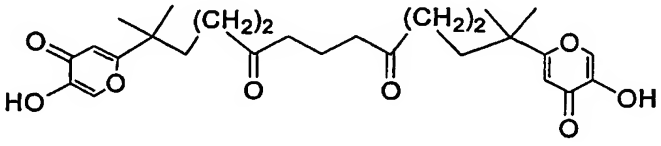
Ib-76

2,14-Bis-(3-hydroxy-isoxazol-4-yl)-2,14-dimethyl-pentadecane-6,10-dione



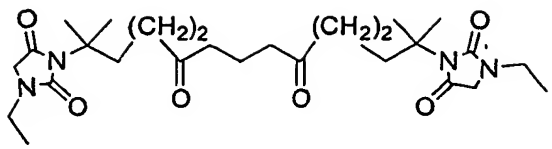
Ib-77

2,14-Bis-(5-hydroxy-4-oxo-4H-pyran-3-yl)-2,14-dimethyl-pentadecane-6,10-dione



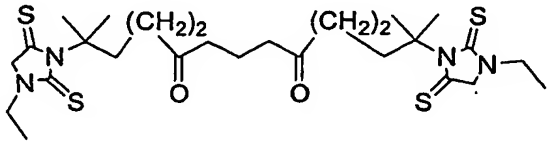
Ib-78

2-(5-Hydroxy-4-oxo-4H-pyran-2-yl)-2,14-dimethyl-14-(5-methyl-4-oxo-4H-pyran-2-yl)-pentadecane-6,10-dione



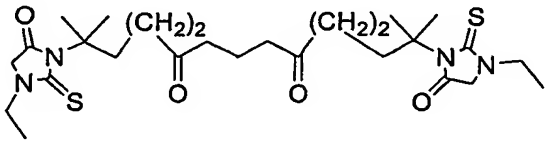
Ib-79

2,14-Bis-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-2,14-dimethyl-pentadecane-6,10-dione



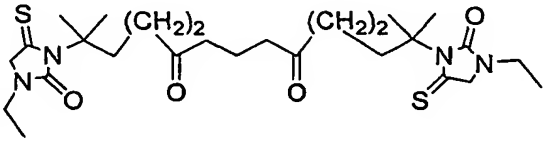
Ib-80

2,14-Bis-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-2,14-dimethyl-pentadecane-6,10-dione



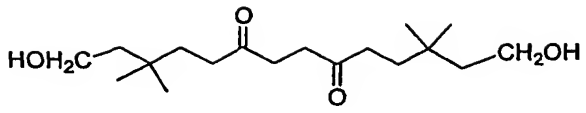
Ib-81

2,14-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-2,14-dimethyl-pentadecane-6,10-dione



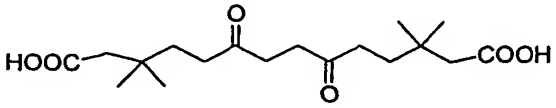
Ib-82

2,14-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-2,14-dimethyl-pentadecane-6,10-dione



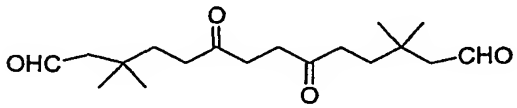
Ib-83

1,14-Dihydroxy-3,3,12,12-tetramethyl-tetradecane-6,9-dione



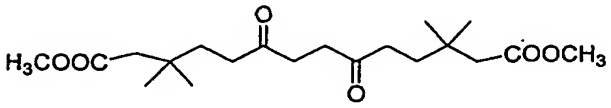
Ib-84

3,3,12,12-Tetramethyl-6,9-dioxo-tetradecanedioic acid



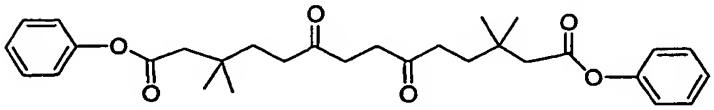
Ib-85

3,3,12,12-Tetramethyl-6,9-dioxo-tetradecanedial



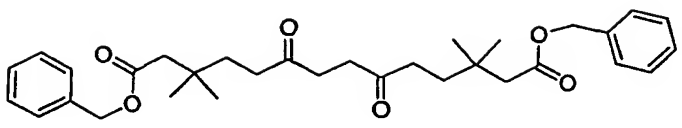
Ib-86

3,3,12,12-Tetramethyl-6,9-dioxo-tetradecanedioic acid dimethyl ester



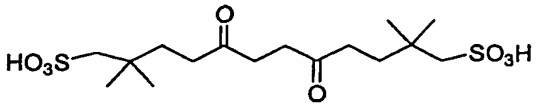
Ib-87

3,3,12,12-Tetramethyl-6,9-dioxo-tetradecanedioic acid diphenyl ester



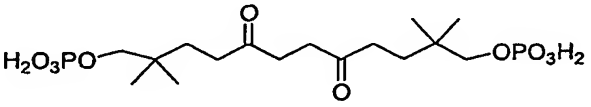
Ib-88

3,3,12,12-Tetramethyl-6,9-dioxo-tetradecanedioic acid dibenzyl ester



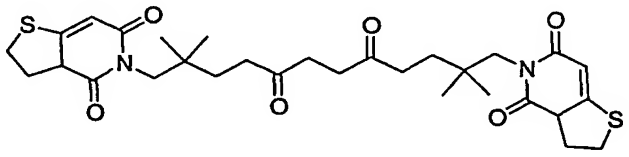
Ib-89

2,2,11,11-Tetramethyl-5,8-dioxo-dodecane-1,12-disulfonic acid



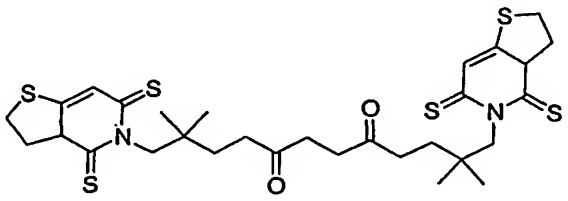
Ib-90

Phosphoric acid mono-(2,2,11,11-tetramethyl-5,8-dioxo-12-phosphonooxy-dodecyl) ester



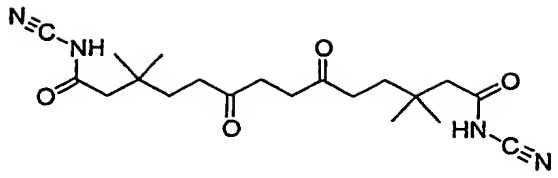
Ib-91

1,12-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dione



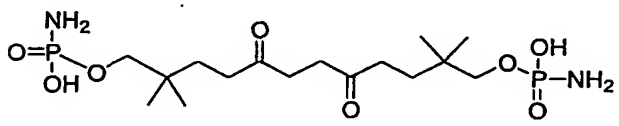
Ib-92

1,12-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dithione



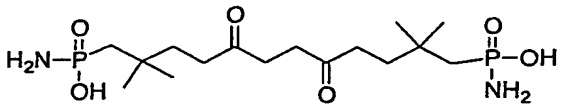
Ib-93

3,3,12,12-Tetramethyl-6,9-dioxo-tetradecanedioic acid dicyanimide



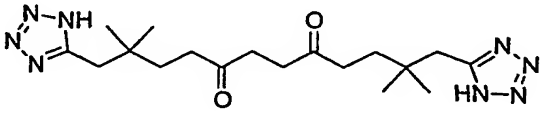
Ib-94

Phosphoramidic acid mono-[12-(amino-hydroxy-phosphoryloxy)-2,2,11,11-tetramethyl-5,8-dioxo-dodecyl] ester



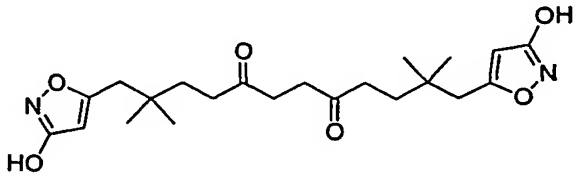
Ib-95

2,2,11,11-Tetramethyl-1,12-bis-(aminohydroxyphosphoryloxy)-dodecane-5,8-dione



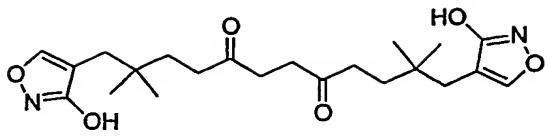
Ib-96

2,2,11,11-Tetramethyl-1,12-bis-(1H-tetrazol-5-yl)-dodecane-5,8-dione



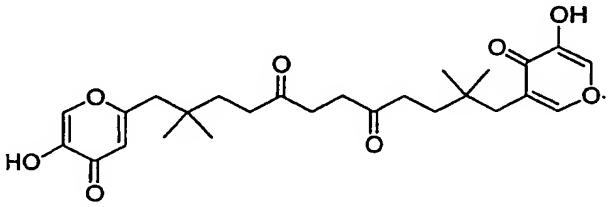
Ib-97

1,12-Bis-(3-hydroxy-isoxazol-5-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dione



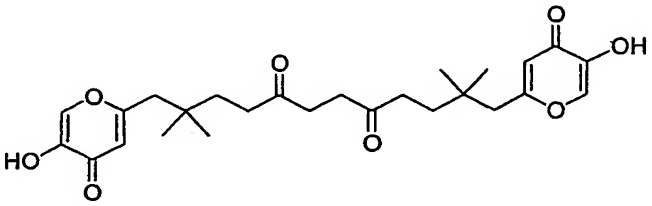
Ib-98

1,12-Bis-(3-hydroxy-isoxazol-4-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dione



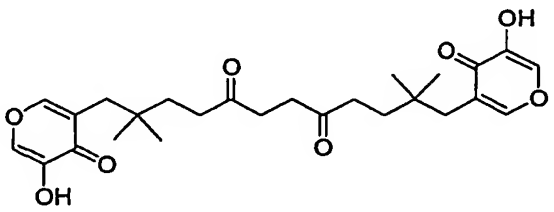
Ib-99

1-(5-Hydroxy-4-oxo-4H-pyran-3-yl)-12-(5-hydroxy-4-oxo-4H-pyran-2-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dione



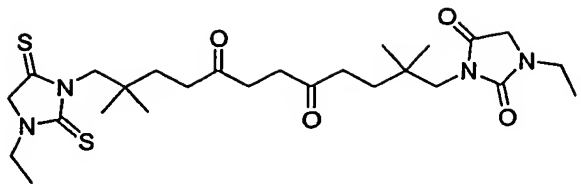
Ib-100

1,12-Bis-(5-hydroxy-4-oxo-4H-pyran-3-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dione



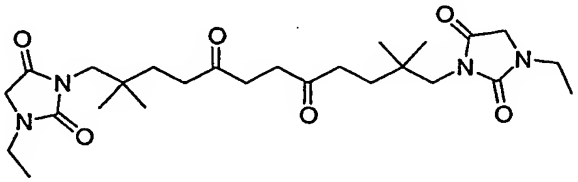
Ib-101

1,12-Bis-(5-hydroxy-4-oxo-4H-pyran-3-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dione



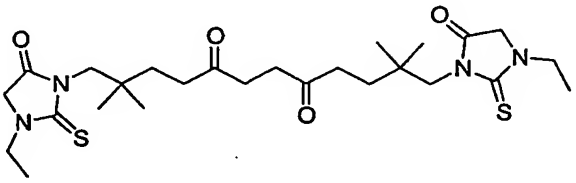
Ib-102

1-Ethyl-3-[12-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-2,2,11,11-tetramethyl-5,8-dioxo-dodecyl]-imidazolidine-2,4-dione



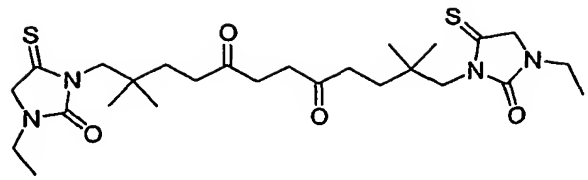
Ib-103

1-Ethyl-3-[12-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-2,2,11,11-tetramethyl-5,8-dioxo-dodecyl]-imidazolidine-2,4-dione



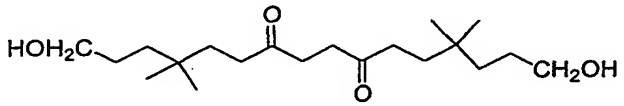
Ib-104

1,12-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dione



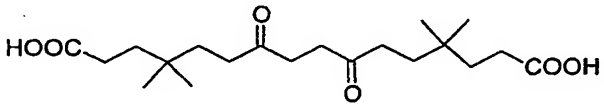
Ib-105

1,12-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dione



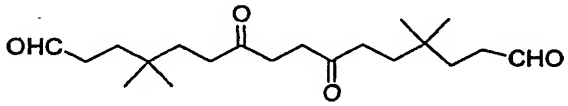
Ib-106

1,16-Dihydroxy-4,4,13,13-tetramethyl-hexadecane-7,10-dione



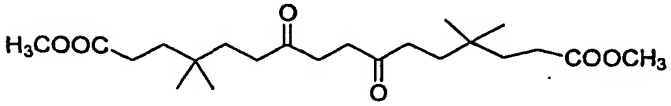
Ib-107

4,4,13,13-Tetramethyl-7,10-dioxo-hexadecanedioic acid



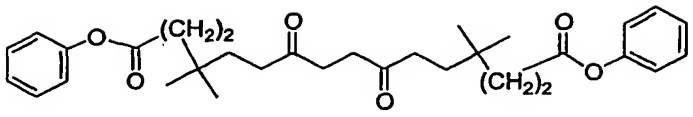
Ib-108

4,4,13,13-Tetramethyl-7,10-dioxo-hexadecanedial



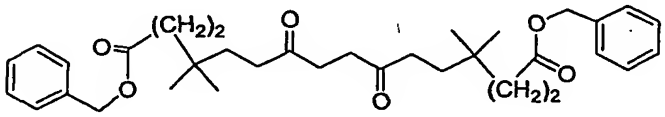
Ib-109

4,4,13,13-Tetramethyl-7,10-dioxo-hexadecanedioic acid dimethyl ester



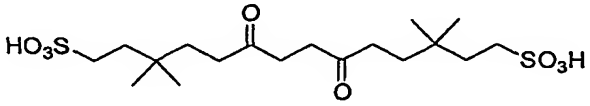
Ib-110

4,4,13,13-Tetramethyl-7,10-dioxo-hexadecanedioic acid diphenyl ester



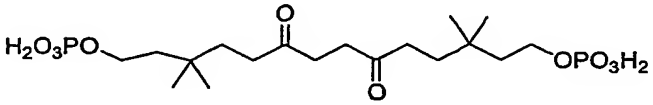
Ib-111

4,4,13,13-Tetramethyl-7,10-dioxo-hexadecanedioic acid dibenzyl ester



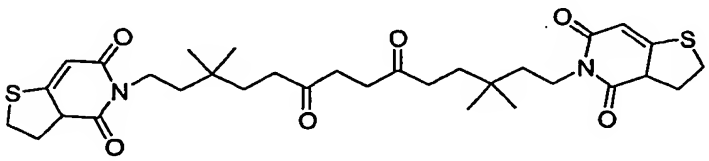
Ib-112

3,3,12,12-Tetramethyl-6,9-dioxo-tetradecane-1,14-disulfonic acid



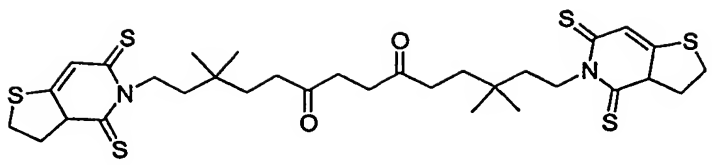
Ib-113

Phosphoric acid mono-(3,3,12,12-tetramethyl-6,9-dioxo-14-phosphonooxy-tetradecyl) ester



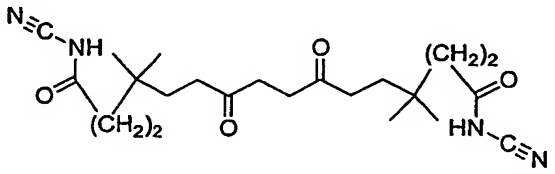
Ib-114

1,14-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione



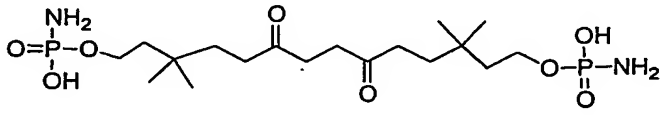
Ib-115

1,14-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione



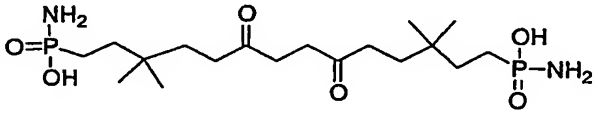
Ib-116

4,4,13,13-Tetramethyl-7,10-dioxo-hexadecanedioic acid dicyanimide



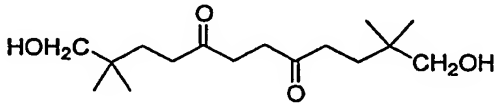
Ib-117

Phosphoramidic acid mono-[14-(amino-hydroxy-phosphoryloxy)-3,3,12,12-tetramethyl-6,9-dioxo-tetradecyl] ester



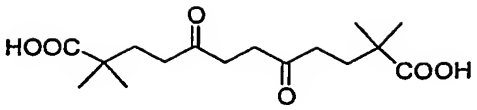
Ib-118

3,3,12,12-Tetramethyl-1,14-bis-(amino-hydroxy-phosphoryloxy)-tetradecane-6,9-dione



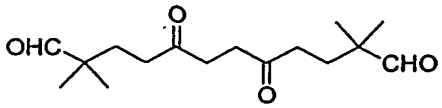
Ib-119

1,12-Dihydroxy-2,2,11,11-tetramethyl-dodecane-5,8-dione



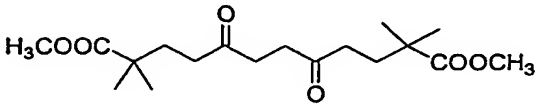
Ib-120

2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid



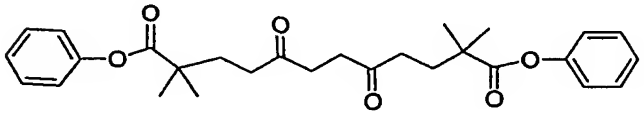
Ib-121

2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedial



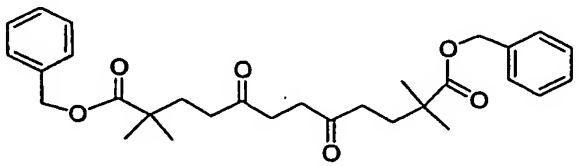
Ib-122

2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid dimethyl ester



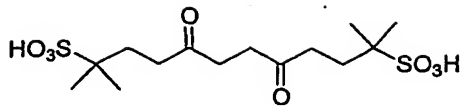
Ib-123

2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid diphenyl ester



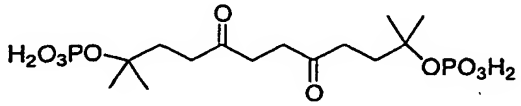
Ib-124

2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid dibenzyl ester



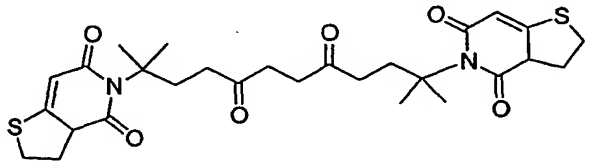
Ib-125

2,11-Dimethyl-5,8-dioxo-dodecane-2,11-disulfonic acid



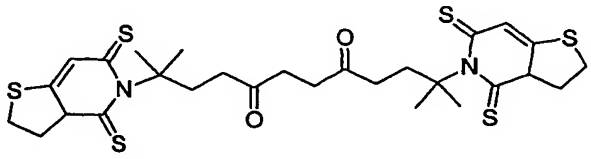
Ib-126

Phosphoric acid mono-(1,1,10-trimethyl-4,7-dioxo-10-phosphonooxy-undecyl) ester



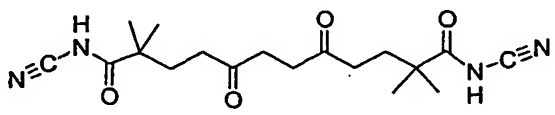
Ib-127

2,11-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,11-dimethyl-dodecane-5,8-dione



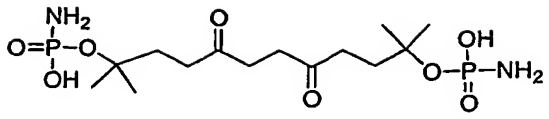
Ib-128

2,11-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,11-dimethyl-dodecane-5,8-dione



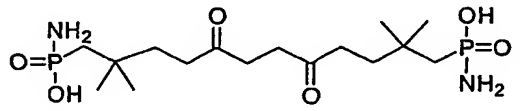
Ib-129

2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid dicyanimide



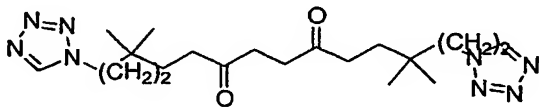
Ib-130

Phosphoramidic acid mono-[10-(amino-hydroxy-phosphoryloxy)-1,1,10-trimethyl-4,7-dioxo-undecyl] ester



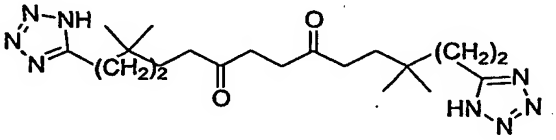
Ib-131

2,2,11,11-Tetramethyl-1,12-(amino-hydroxy-phosphoryloxy)-dodecane-5,8-dione



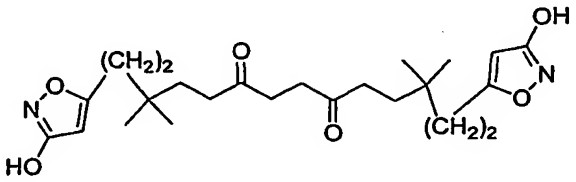
Ib-132

3,3,12,12-Tetramethyl-1,14-bis-tetrazol-1-yl-tetradecane-6,9-dione



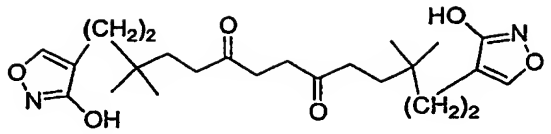
Ib-133

3,3,12,12-Tetramethyl-1,14-bis-(1H-tetrazol-5-yl)-tetradecane-6,9-dione



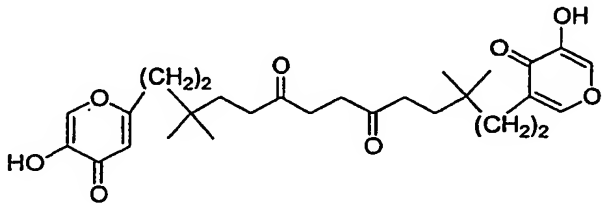
Ib-134

1,14-Bis-(3-hydroxy-isoxazol-5-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione



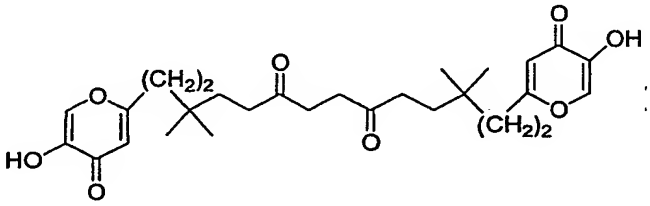
Ib-135

1,14-Bis-(3-hydroxy-isoxazol-4-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione



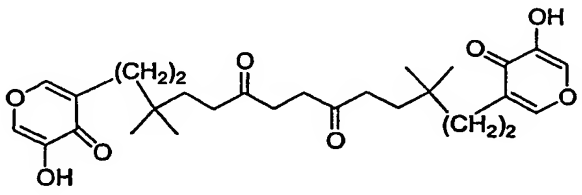
Ib-136

1-(5-Hydroxy-4-oxo-4H-pyran-2-yl)-14-(5-hydroxy-4-oxo-4H-pyran-3-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione



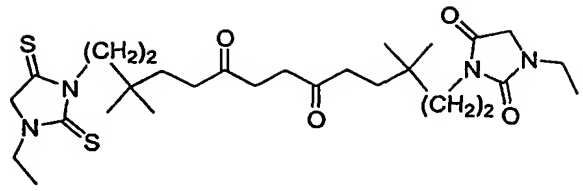
Ib-137

1,14-Bis-(5-hydroxy-4-oxo-4H-pyran-2-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione



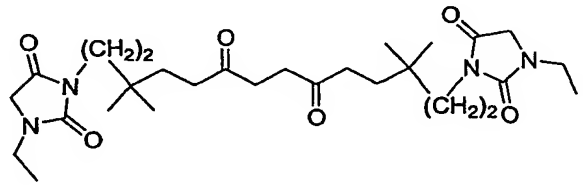
Ib-138

1,14-Bis-(5-hydroxy-4-oxo-4H-pyran-3-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione



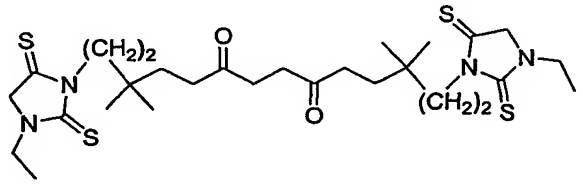
Ib-139

1-Ethyl-3-[14-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-3,3,12,12-tetramethyl-6,9-dioxo-tetradecyl]-imidazolidine-2,4-dione



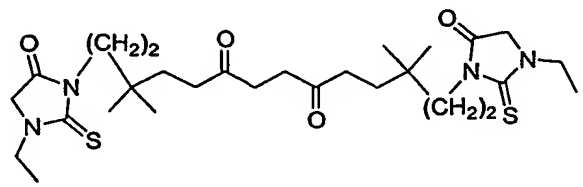
Ib-140

1-Ethyl-3-[14-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-3,3,12,12-tetramethyl-6,9-dioxo-tetradecyl]-imidazolidine-2,4-dione



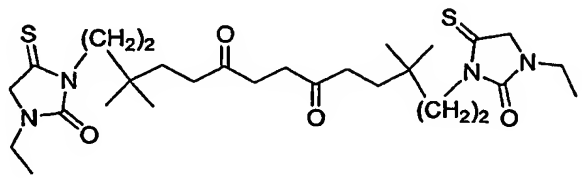
Ib-141

1-Ethyl-3-[14-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-3,3,12,12-tetramethyl-6,9-dioxo-tetradecyl]-imidazolidine-2,4-dithione



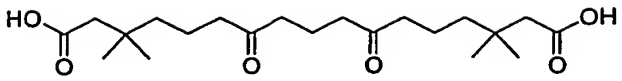
Ib-142

1,14-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione



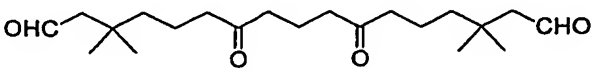
Ib-143

1,14-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione



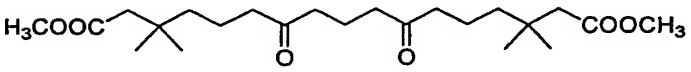
Ib-144

1,17-Dihydroxy-3,3,15,15-tetramethyl-heptadecane-7,11-dione



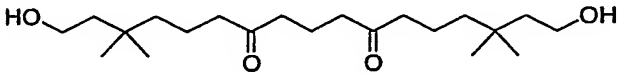
Ib-145

3,3,15,15-Tetramethyl-7,11-dioxo-heptadecanedial



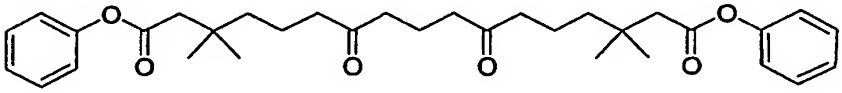
Ib-146

3,3,15,15-Tetramethyl-7,11-dioxo-heptadecanedioic acid dimethyl ester



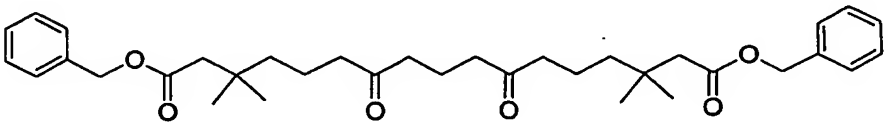
Ib-147

1,17-Dihydroxy-3,3,15,15-tetramethyl-heptadecane-7,11-dione



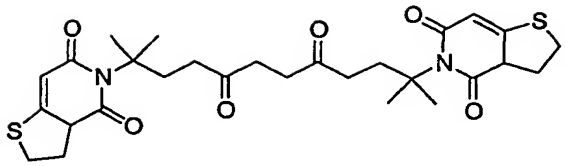
Ib-148

3,3,15,15-Tetramethyl-7,11-dioxo-heptadecanedioic acid diphenyl ester



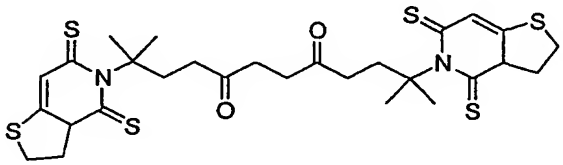
Ib-149

3,3,15,15-Tetramethyl-7,11-dioxo-heptadecanedioic acid dibenzyl ester



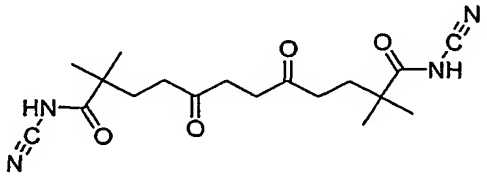
Ib-150

2,11-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,11-dimethyl-dodecane-5,8-dione



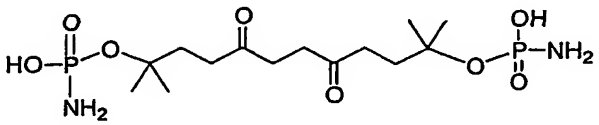
Ib-151

2,11-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,11-dimethyl-dodecane-5,8-dione



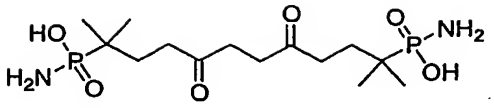
Ib-152

2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid dicyanamide



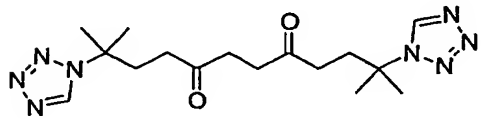
Ib-153

Phosphoramidic acid mono-[10-(amino-hydroxy-phosphoryloxy)-1,1,10-trimethyl-4,7-dioxo-undecyl] ester



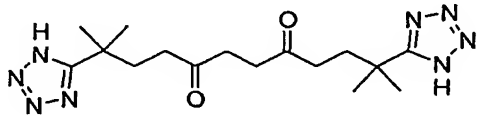
Ib-154

2,11-Dimethyl-2,11-bis-(amino-hydroxy-phosphoryloxy)-dodecane-5,8-dione



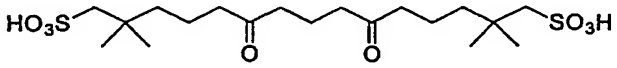
Ib-155

2,11-Dimethyl-2,11-bis-tetrazol-1-yl-dodecane-5,8-dione



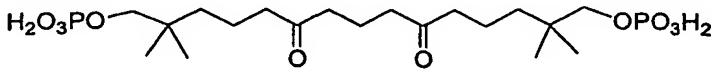
Ib-156

2,11-Dimethyl-2,11-bis-(1H-tetrazol-5-yl)-dodecane-5,8-dione



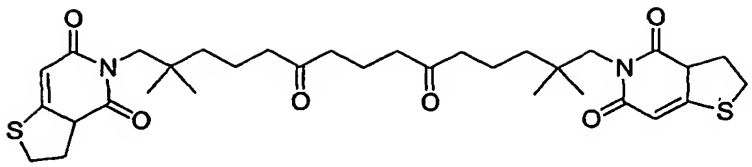
Ib-157

2,2,14,14-Tetramethyl-6,10-dioxo-pentadecane-1,15-disulfonic acid



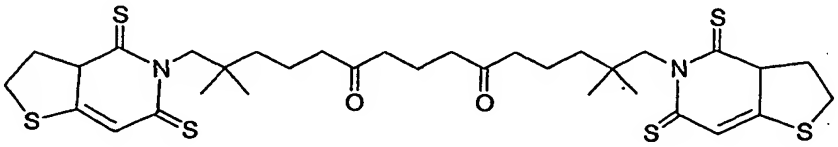
Ib-158

Phosphoric acid mono-(2,2,14,14-tetramethyl-6,10-dioxo-15-phosphonooxy-pentadecyl) ester



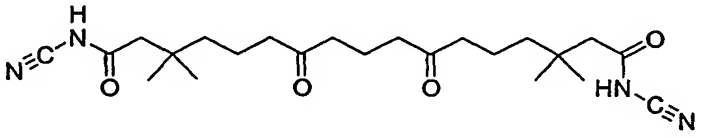
Ib-159

1,15-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione



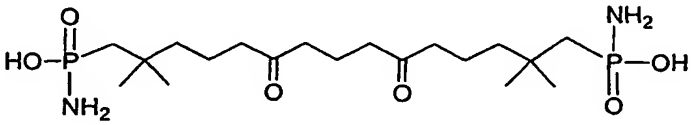
Ib-160

1,15-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione



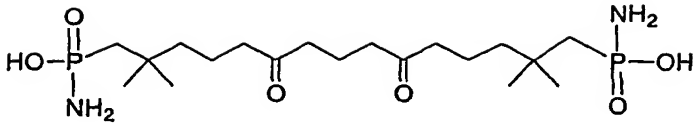
Ib-161

3,3,15,15-Tetramethyl-7,11-dioxo-heptadecanedioic acid dicyanamide



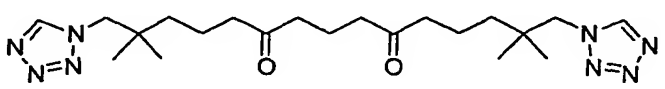
Ib-162

Phosphoramidic acid mono-[16-(amino-hydroxy-phosphoryloxy)-4,4,15,15-tetramethyl-7,11-dioxo-hexadecyl] ester



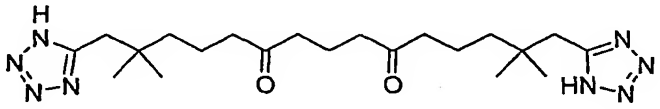
Ib-163

2,2,14,14-Tetramethyl-1,15-bis-(amino-hydroxy-phosphoryloxy)-pentadecane-6,10-dione



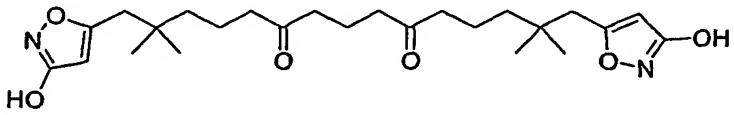
Ib-164

2,2,14,14-Tetramethyl-1,15-bis-tetrazol-1-yl-pentadecane-6,10-dione



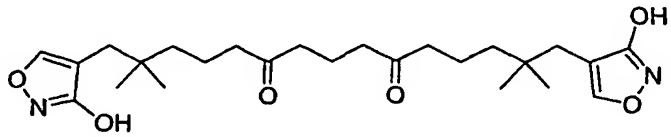
Ib-165

2,2,14,14-Tetramethyl-1,15-bis-(1H-tetrazol-5-yl)-pentadecane-6,10-dione



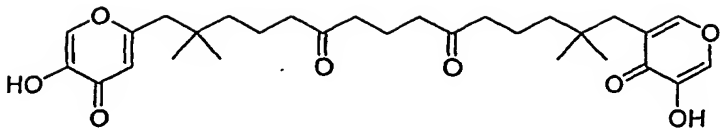
Ib-166

1,15-Bis-(3-hydroxy-isoxazol-5-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione



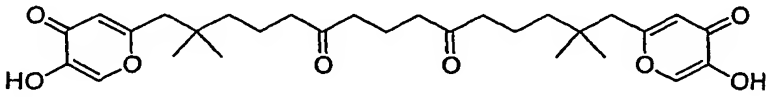
Ib-167

1,15-Bis-(3-hydroxy-isoxazol-4-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione



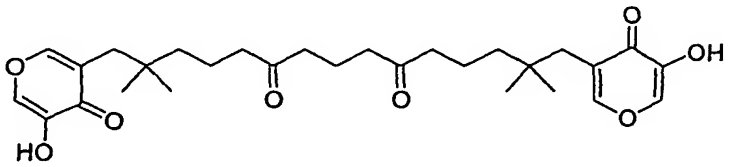
Ib-168

1-(5-Hydroxy-4-oxo-4H-pyran-3-yl)-15-(5-hydroxy-4-oxo-4H-pyran-2-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione



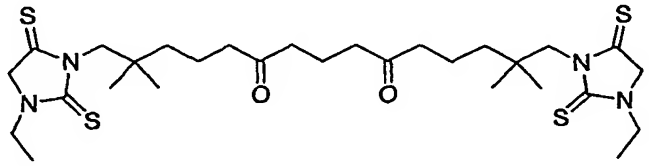
Ib-169

1,15-Bis-(5-hydroxy-4-oxo-4H-pyran-2-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione



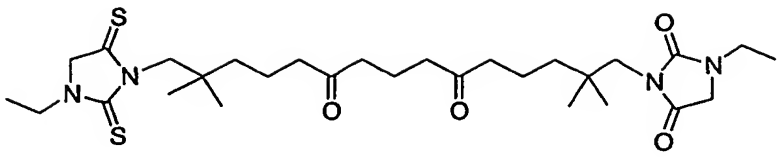
Ib-170

1,15-Bis-(5-hydroxy-4-oxo-4H-pyran-3-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione



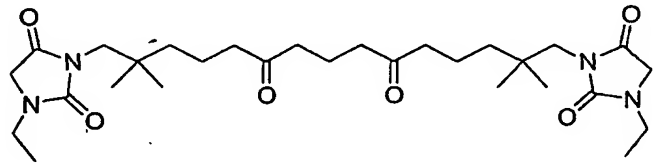
Ib-171

1,15-Bis-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione



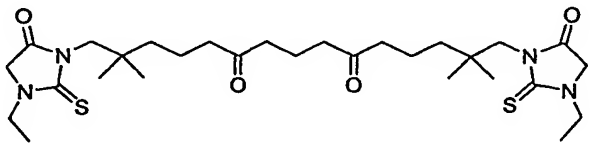
Ib-172

1-Ethyl-3-[15-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-2,2,14,14-tetramethyl-6,10-dioxo-pentadecyl]-imidazolidine-2,4-dione



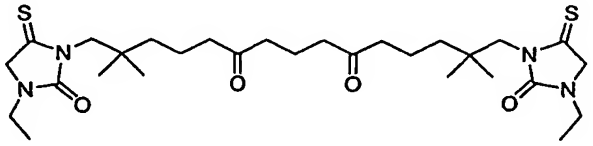
Ib-173

1,15-Bis-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione



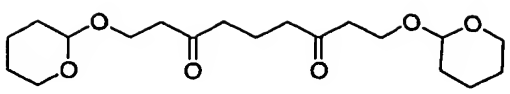
Ib-174

1,15-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione



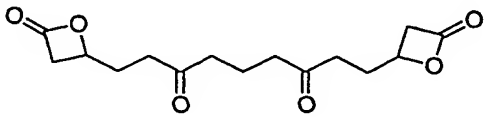
Ib-175

1,15-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione



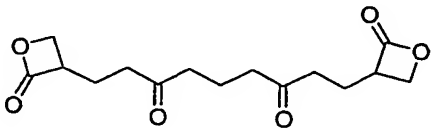
Ic-1

1,9-Bis-(tetrahydro-pyran-2-yloxy)-nonane-3,7-dione



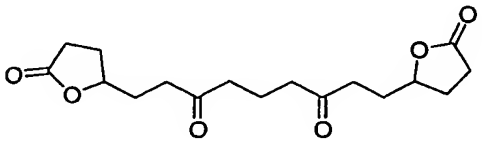
Ic-2

1,9-Bis-(4-oxo-oxetan-2-yl)-nonane-3,7-dione



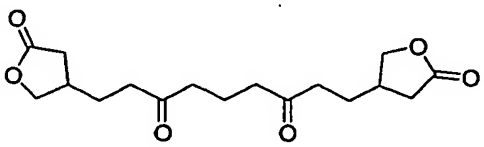
Ic-3

1,9-Bis-(2-oxo-oxetan-3-yl)-nonane-3,7-dione



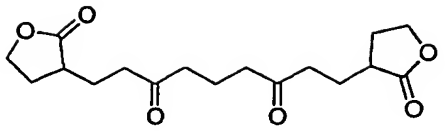
Ic-4

1,9-Bis-(5-oxo-tetrahydrofuran-2-yl)-nonane-3,7-dione



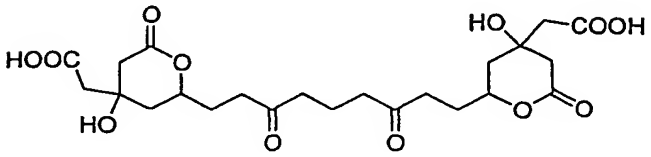
Ic-5

1,9-Bis-(5-oxo-tetrahydrofuran-3-yl)-nonane-3,7-dione



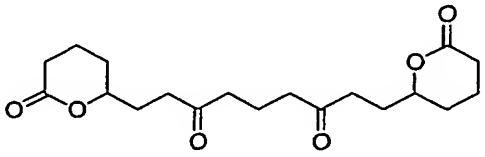
Ic-6

1,9-Bis-(2-oxo-tetrahydrofuran-3-yl)-nonane-3,7-dione



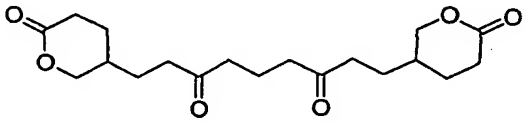
Ic-7

{2-[9-(4-Carboxymethyl-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-3,7-dioxo-nonyl]-4-hydroxy-6-oxo-tetrahydropyran-4-yl}-acetic acid



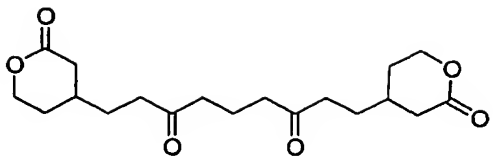
Ic-8

1,9-Bis-(6-oxo-tetrahydropyran-2-yl)-nonane-3,7-dione



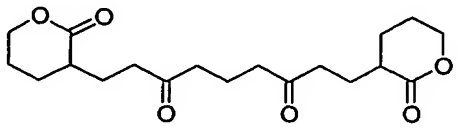
Ic-9

1,9-Bis-(6-oxo-tetrahydropyran-3-yl)-nonane-3,7-dione



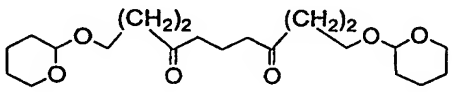
Ic-10

1,9-Bis-(2-oxo-tetrahydropyran-4-yl)-nonane-3,7-dione



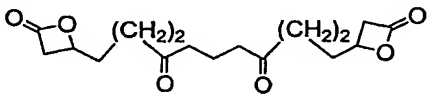
Ic-11

1,9-Bis-(2-oxo-tetrahydropyran-3-yl)-nonane-3,7-dione



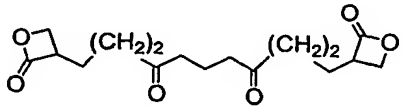
Ic-12

1,11-Bis-(tetrahydro-pyran-2-yloxy)-undecane-4,8-dione



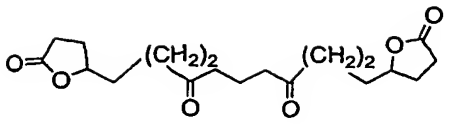
Ic-13

1,11-Bis-(2-oxo-oxetan-3-yl)-undecane-4,8-dione



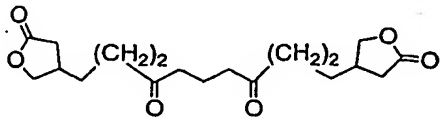
Ic-14

1,11-Bis-(2-oxo-oxetan-3-yl)-undecane-4,8-dione



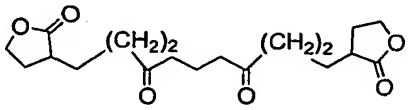
Ic-15

1,11-Bis-(5-oxo-tetrahydrofuran-2-yl)-undecane-4,8-dione



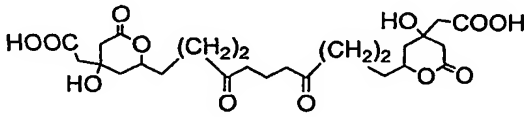
Ic-16

1,11-Bis-(5-oxo-tetrahydrofuran-3-yl)-undecane-4,8-dione



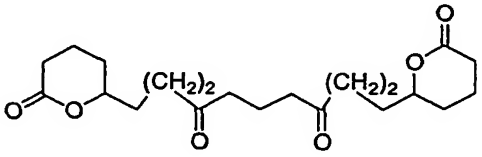
Ic-17

1,11-Bis-(2-oxo-tetrahydrofuran-3-yl)-undecane-4,8-dione



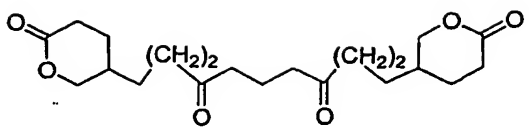
Ic-18

{2-[11-(4-Carboxymethyl-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-4,8-dioxo-undecyl]-4-hydroxy-6-oxo-tetrahydropyran-4-yl}-acetic acid



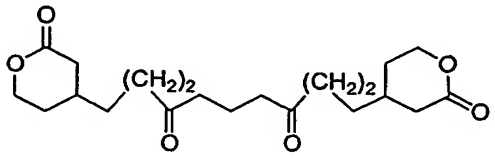
Ic-19

1,11-Bis-(6-oxo-tetrahydropyran-2-yl)-undecane-4,8-dione



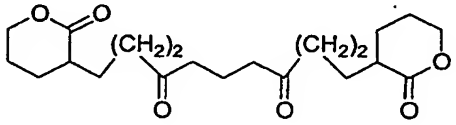
Ic-20

1,11-Bis-(6-oxo-tetrahydropyran-3-yl)-undecane-4,8-dione



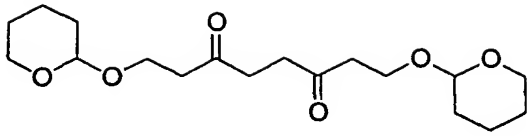
Ic-21

1,11-Bis-(2-oxo-tetrahydropyran-4-yl)-undecane-4,8-dione



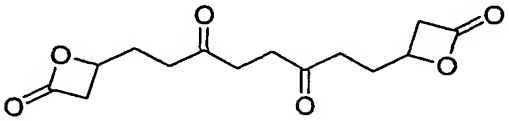
Ic-22

1,11-Bis-(2-oxo-tetrahydropyran-3-yl)-undecane-4,8-dione



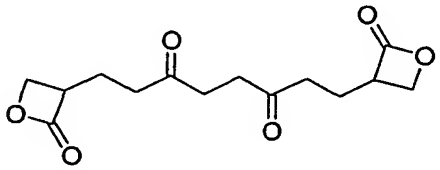
IC-23

1,8-Bis-(tetrahydropyran-2-yloxy)-octane-3,6-dione



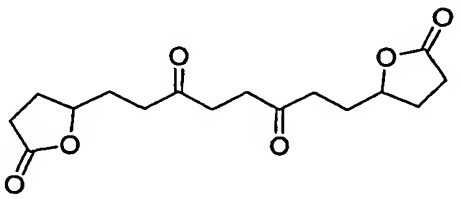
IC-24

1,8-Bis-(4-oxo-oxetan-2-yl)-octane-3,6-dione



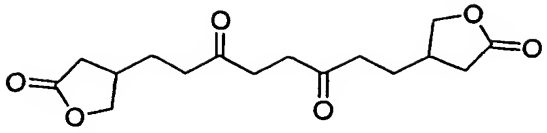
IC-25

1,8-Bis-(2-oxo-oxetan-3-yl)-octane-3,6-dione



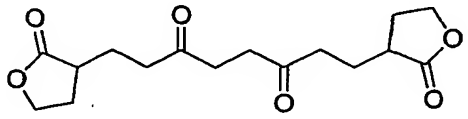
IC-26

1,8-Bis-(5-oxo-tetrahydro-furan-2-yl)-octane-3,6-dione



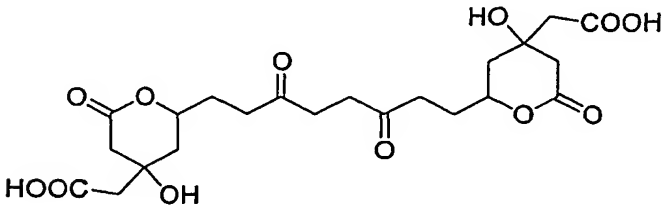
IC-27

1,8-Bis-(5-oxo-tetrahydro-furan-3-yl)-octane-3,6-dione



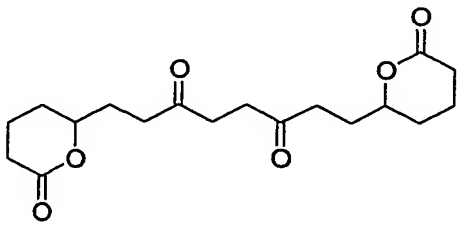
IC-28

1,8-Bis-(2-oxo-tetrahydro-furan-3-yl)-octane-3,6-dione



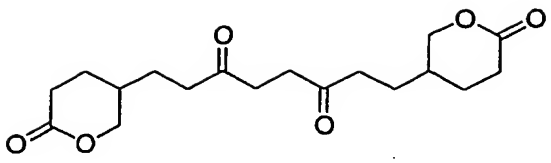
IC-29

{2-[8-(4-Carboxymethyl-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-3,6-dioxo-octyl]-4-hydroxy-6-oxo-tetrahydro-pyran-4-yl}-acetic acid



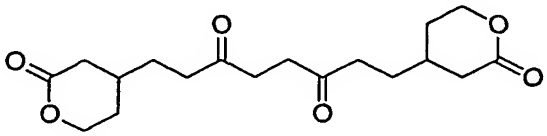
IC-30

1,8-Bis-(6-oxo-tetrahydropyran-2-yl)-octane-3,6-dione



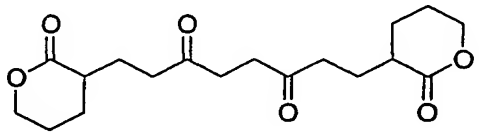
IC-31

1,8-Bis-(6-oxo-tetrahydropyran-3-yl)-octane-3,6-dione



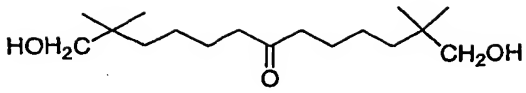
IC-32

1,8-Bis-(2-oxo-tetrahydropyran-4-yl)-octane-3,6-dione



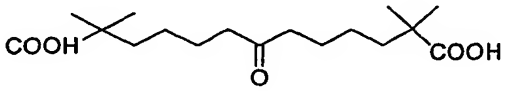
IC-33

1,8-Bis-(2-oxo-tetrahydropyran-3-yl)-octane-3,6-dione



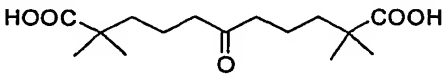
II-1

1,13-Dihydroxy-2,2,12,12-tetramethyl-tridecan-7-one



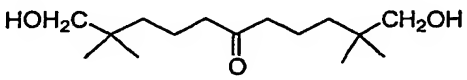
II-2

12-Hydroxy-2,2,12-trimethyl-7-oxo-tridecanoic acid; compound with formaldehyde



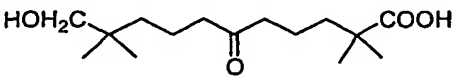
II-3

11-Hydroperoxy-2,2,10,10-tetramethyl-6-oxo-undecanoic acid



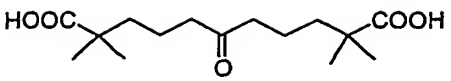
II-4

1,11-Dihydroxy-2,2,10,10-tetramethyl-undecan-6-one



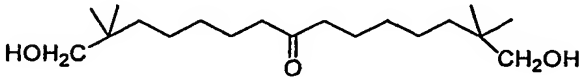
II-5

11-Hydroxy-2,2,10,10-tetramethyl-6-oxo-undecanoic acid



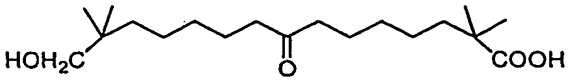
II-6

2,2,10,10-Tetramethyl-6-oxo-undecanedioic acid



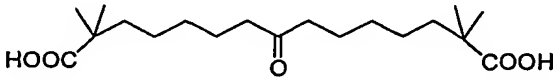
II-7

1,15-Dihydroxy-2,2,14,14-tetramethyl-pentadecan-8-one



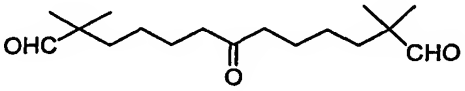
II-8

15-Hydroxy-2,2,14,14-tetramethyl-8-oxo-pentadecanoic acid



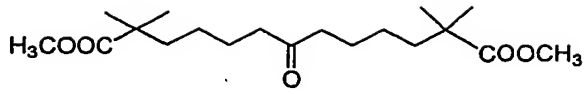
II-9

2,2,14,14-Tetramethyl-8-oxo-pentadecanedioic acid



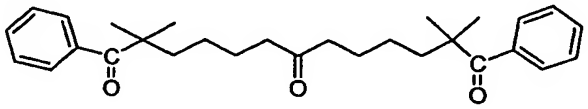
II-10

2,2,12,12-Tetramethyl-7-oxo-tridecanedial



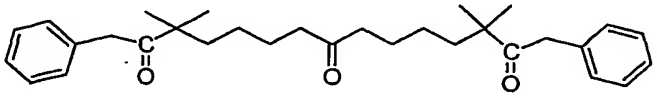
II-11

2,2,12,12-Tetramethyl-7-oxo-tridecanedioic acid dimethyl ester



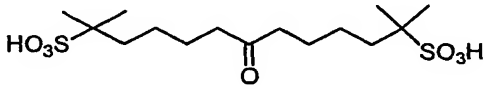
II-12

2,2,12,12-Tetramethyl-1,13-diphenyl-tridecane-1,7,13-trione



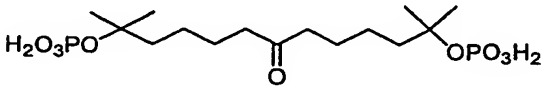
II-13

3,3,13,13-Tetramethyl-1,15-diphenyl-pentadecane-2,8,14-trione



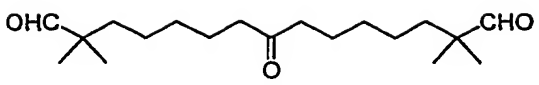
II-14

2,12-Dimethyl-7-oxo-tridecane-2,12-disulfonic acid



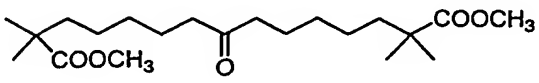
II-15

Phosphoric acid mono-(1,1,11-trimethyl-6-oxo-11-phosphonooxy-dodecyl) ester



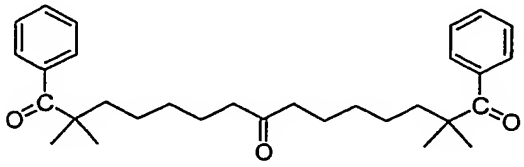
II-16

2,2,14,14-Tetramethyl-8-oxo-pentadecanedial



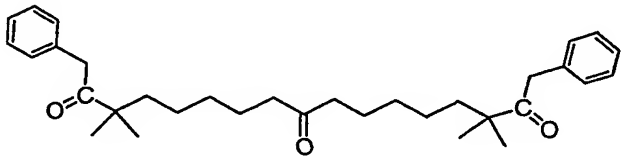
II-17

2,2,14,14-Tetramethyl-8-oxo-pentadecanedioic acid dimethyl ester



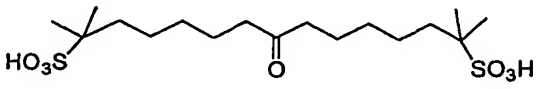
II-18

2,2,14,14-Tetramethyl-1,15-diphenyl-pentadecane-1,8,15-trione



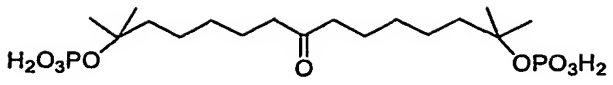
II-19

3,3,15,15-Tetramethyl-1,17-diphenyl-heptadecane-2,9,16-trione



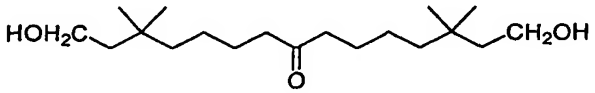
II-20

2,14-Dimethyl-8-oxo-pentadecane-2,14-disulfonic acid



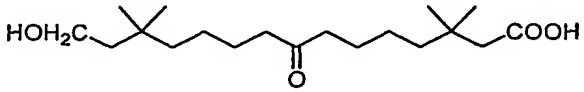
II-21

Phosphoric acid mono-(1,1,13-trimethyl-7-oxo-13-phosphonooxy-tetradecyl) ester



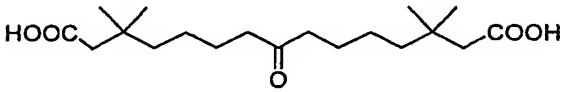
II-22

1,15-Dihydroxy-3,3,13,13-tetramethyl-pentadecan-8-one



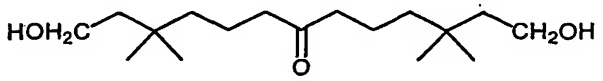
II-23

15-Hydroxy-3,3,13,13-tetramethyl-8-oxo-pentadecanoic acid



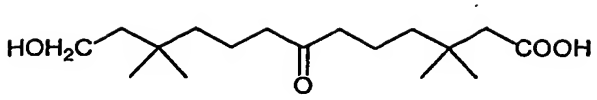
II-24

3,3,13,13-Tetramethyl-8-oxo-pentadecanedioic acid



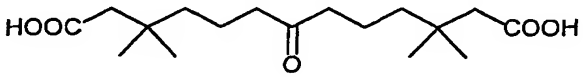
II-25

1,13-Dihydroxy-3,3,11,11-tetramethyl-tridecan-7-one



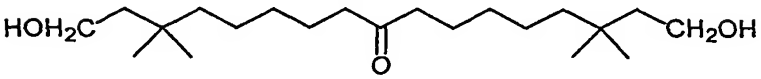
II-26

13-Hydroxy-3,3,11,11-tetramethyl-7-oxo-tridecanoic acid



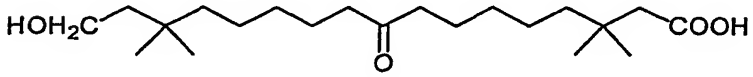
II-27

3,3,11,11-Tetramethyl-7-oxo-tridecanedioic acid



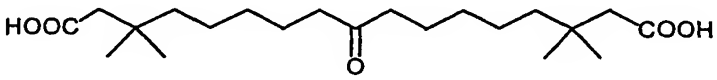
II-28

1,17-Dihydroxy-3,3,15,15-tetramethyl-heptadecan-9-one



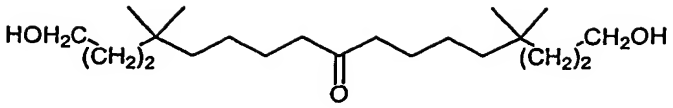
II-29

17-Hydroxy-3,3,15,15-tetramethyl-9-oxo-heptadecanoic acid



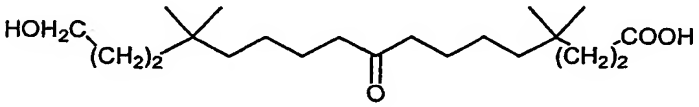
II-30

3,3,15,15-Tetramethyl-9-oxo-heptadecanedioic acid



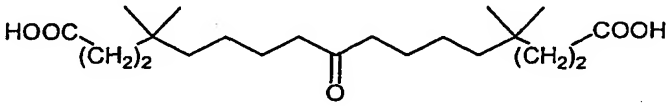
II-31

1,17-Dihydroxy-4,4,14,14-tetramethyl-heptadecan-9-one



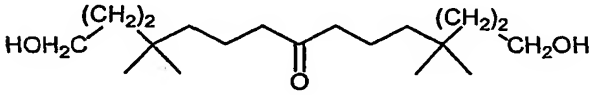
II-32

17-Hydroxy-4,4,14,14-tetramethyl-9-oxo-heptadecanoic acid



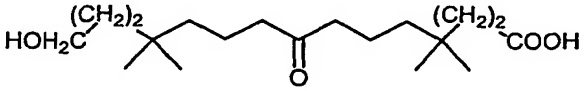
II-33

4,4,14,14-Tetramethyl-heptadecan-9-oxo-1,17-dicarboxylic acid



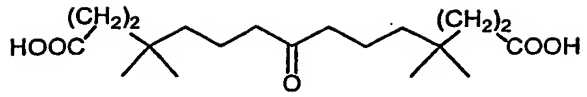
II-34

1,15-Dihydroxy-4,4,14,14-tetramethyl-pentadecan-8-one



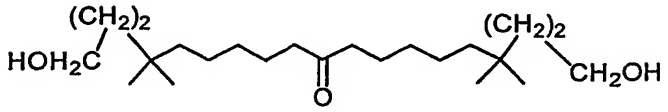
II-35

15-Hydroxy-4,4,12,12-tetramethyl-8-oxo-pentadecanoic acid



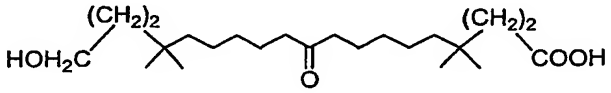
II-36

4,4,12,12-Tetramethyl-8-oxo-pentadecanedioic acid



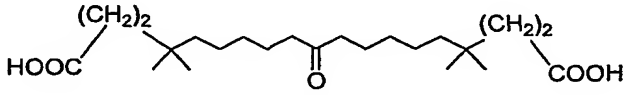
II-37

1,19-Dihydroxy-4,4,16,16-tetramethyl-nonadecan-10-one



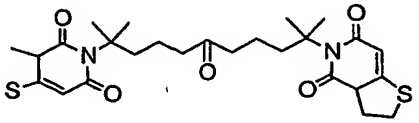
II-38

19-Hydroxy-4,4,16,16-tetramethyl-10-oxo-nonadecanoic acid



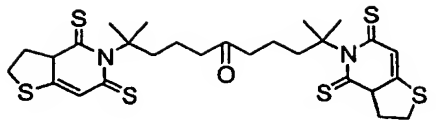
II-39

4,4,16,16-Tetramethyl-10-oxo-nonadecanedioic acid



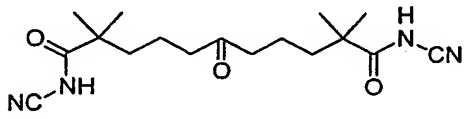
II-40

5-[9-(4-Mercapto-3-methyl-2,6-dioxo-3,6-dihydro-2H-pyridin-1-yl)-1,1,9-trimethyl-5-oxo-decyl]-3,3a-dihydro-2H-thieno[3,2-c]pyridine-4,6-dione



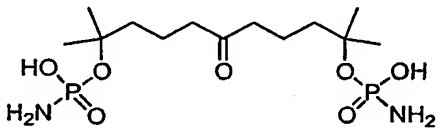
II-41

2,10-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,10-dimethyl-undecan-6-one



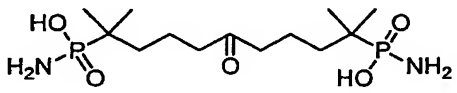
II-42

2,2,10,10-Tetramethyl-6-oxo-undecanedioic acid bis-cyanoamide



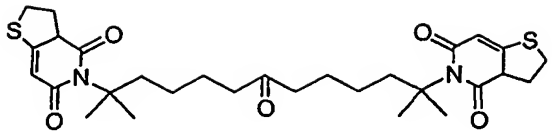
II-43

Phosphoramidic acid mono-[9-(amino-hydroxy-phosphoryloxy)-1,1,9-trimethyl-5-oxo-decyl] ester



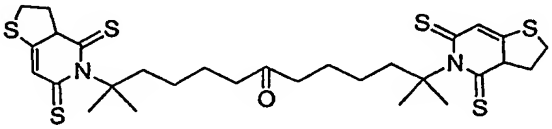
II-44

Phosphoramidic acid mono-[9-(amino-hydroxy-phosphoryloxy)-1,1,9-trimethyl-5-oxo-decyl] ester



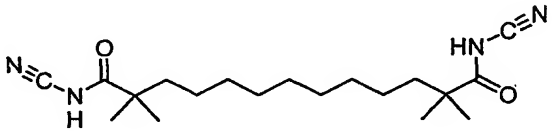
II-45

2,12-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,12-dimethyl-tridecan-7-one



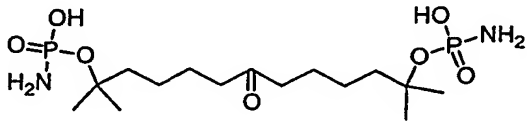
II-46

2,12-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-*c*]pyridi-5-yl)-2,12-dimehyl-tridecan-7-one



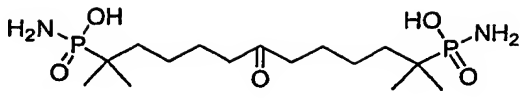
II-47

2,2,12,12-Tetramethyl-7-oxo-tridecanedioic acid bis-cyanoamide



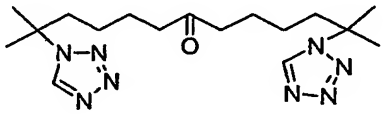
II-48

Phosphoramidic acid mono-[11-(amino-hydroxy-phosphoryloxy)-1,1,11-trimethyl-6-oxo-dodecyl] ester



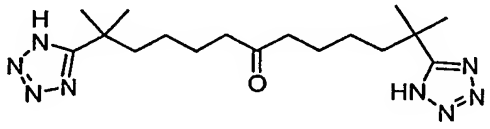
II-49

Phosphoramidic acid mono-[11(amino-hydroxy-phosphoryloxy)-1,1,11-trimethyl-6-oxo-dodecyl] ester



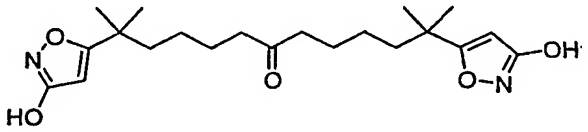
II-50

2,12-Dimethyl-2,12-bis-tetrazol-1-yl-tridecan-7-one



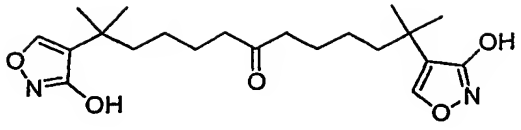
II-51

2,12-Dimethyl-2,12-bis-(1H-tetrazol-5-yl)-tridecan-7-one



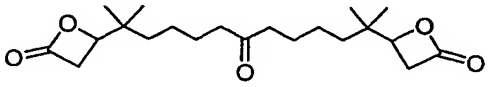
II-52

2,12-Bis-(3-hydroxy-isoxazol-5-yl)-2,12-dimethyl-tridecan-7-one



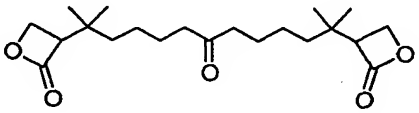
II-53

2,12-Bis-(3-hydroxy-isoxazol-4-yl)-2,12-dimethyl-tridecan-7-one



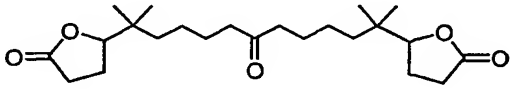
II-54

4-[11-(4-oxo-oxetan-2-yl)-1,1,11-Trimethyl-6-oxo-dodecyl]-oxetan-2-one



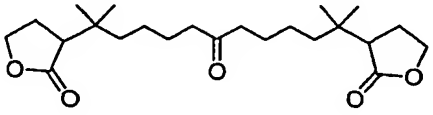
II-55

3-[11-(4-oxo-oxetan-2-yl)-1,1,11-Trimethyl-6-oxo-dodecyl]-oxetan-2-one



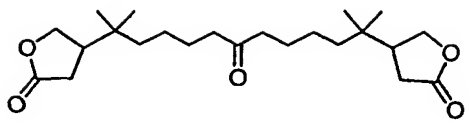
II-56

5-[11-(5-oxo-tetrahydro-furan-3-yl)-1,1,11-Trimethyl-6-oxo-dodecyl]-dihydro-furan-2-one



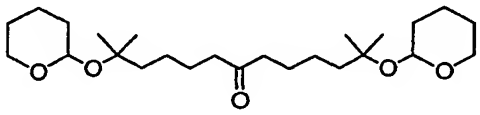
II-57

3-[11-(5-oxo-tetrahydro-furan-3-yl)-1,1,11-Trimethyl-6-oxo-dodecyl]-dihydro-furan-2-one



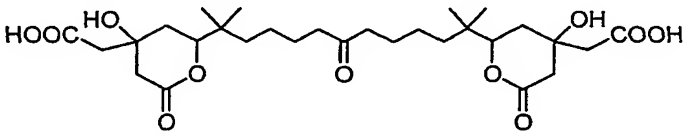
II-58

4-[11-(5-oxo-tetrahydro-furan-3-yl)-1,1,11-Trimethyl-6-oxo-dodecyl]-dihydro-furan-2-one



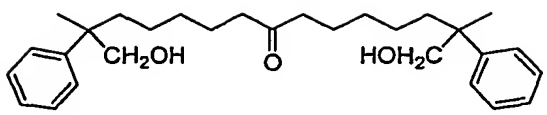
II-59

2,12-Dimethyl-2,12-bis-(tetrahydro-pyran-2-yloxy)-tridecan-7-one



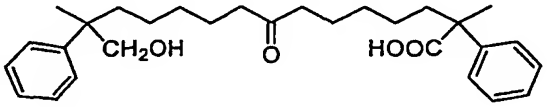
II-60

{2-[11-(4-Carboxymethyl-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-1,1,11-trimethyl-6-oxo-dodecyl]-4-hydroxy-6-oxo-tetrahydro-pyran-4-yl}-acetic acid



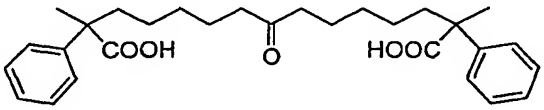
IIa-1

1,15-Dihydroxy-2,14-dimethyl-2,14-diphenyl-pentadecan-8-one



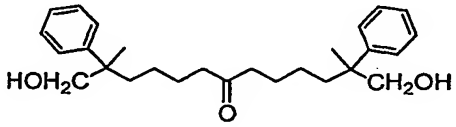
IIa-2

15-Hydroxy-2,14-dimethyl-8-oxo-2,14-diphenyl-pentadecanoic acid



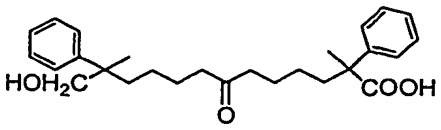
IIa-3

2,14-Dimethyl-8-oxo-2,14-diphenyl-pentadecanedioic acid



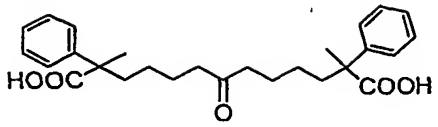
IIa-4

1,13-Dihydroxy-2,12-dimethyl-2,12-diphenyl-tridecan-7-one



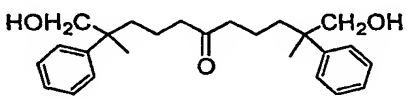
IIa-5

13-Hydroxy-2,12-dimethyl-7-oxo-2,12-diphenyl-tridecanoic acid



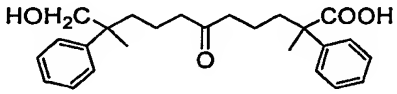
IIa-6

2,12-Dimethyl-7-oxo-2,12-diphenyl-tridecanedioic acid



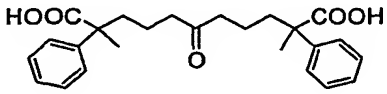
IIa-7

1,11-Dihydroxy-2,10-dimethyl-2,10-diphenyl-undecan-6-one



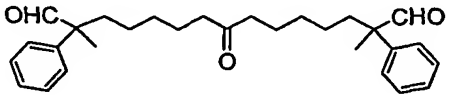
IIa-8

11-Hydroxy-2,10-dimethyl-6-oxo-2,10-diphenyl-undecanoic acid



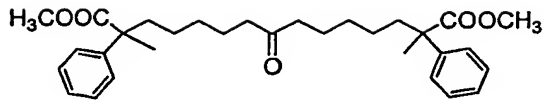
IIa-9

2,10-Dimethyl-6-oxo-2,10-diphenyl-undecanedioic acid



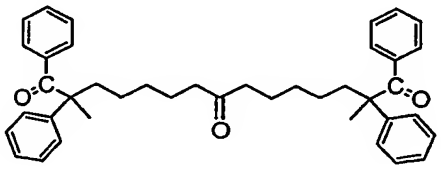
IIa-10

2,14-Dimethyl-8-oxo-2,14-diphenyl-pentadecanedial



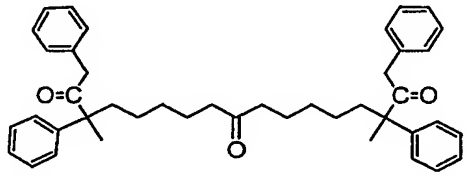
IIa-11

2,14-Dimethyl-8-oxo-2,14-diphenyl-pentadecanedioic acid dimethyl ester



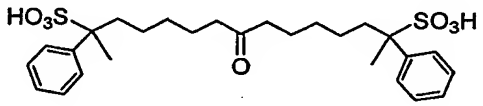
IIa-12

2,14-Dimethyl-1,2,14,15-tetraphenyl-pentadecane-1,8,15-trione



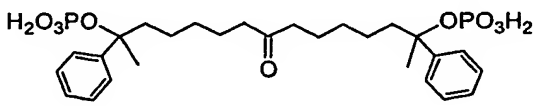
IIa-13

3,15-Dimethyl-1,3,15,17-tetraphenyl-heptadecane-2,9,16-trione



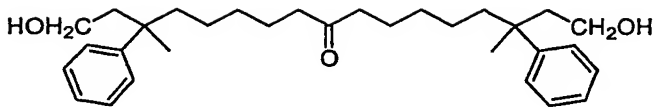
IIa-14

8-Oxo-2,14-diphenyl-pentadecane-2,14-disulfonic acid



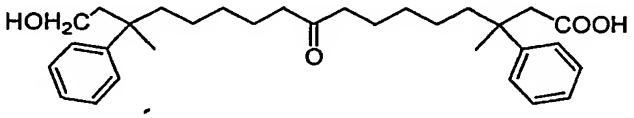
IIa-15

Phosphoric acid mono-(1-methyl-7-oxo-1,13-diphenyl-13-phosphonooxy-tetradecyl) ester



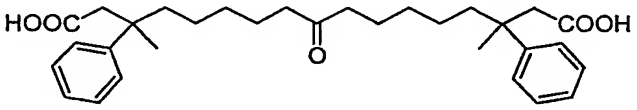
IIa-16

1,17-Dihydroxy-3,15-dimethyl-3,15-diphenyl-heptadecan-9-one



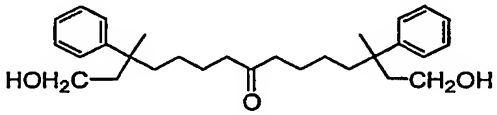
IIa-17

17-Hydroxy-3,15-dimethyl-9-oxo-3,15-diphenyl-heptadecanoic acid



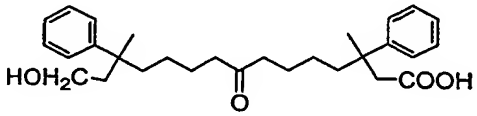
IIa-18

3,15-Dimethyl-9-oxo-3,15-diphenyl-heptadecanedioic acid



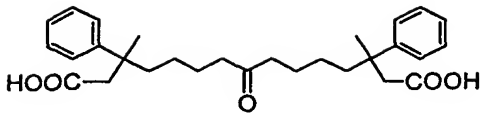
IIa-19

1,15-Dihydroxy-3,13-dimethyl-3,13-diphenyl-pentadecan-8-one



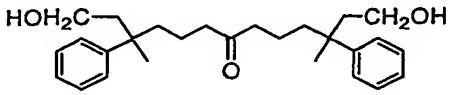
IIa-20

15-Hydroxy-3,13-dimethyl-8-oxo-3,13-diphenyl-pentadecanoic acid



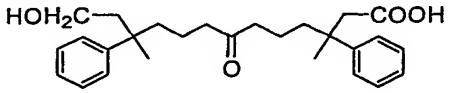
IIa-21

3,13-Dimethyl-8-oxo-3,13-diphenyl-pentadecanedioic acid



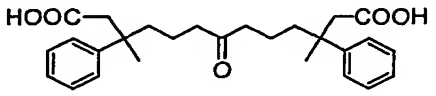
IIa-22

1,13-Dihydroxy-3,11-dimethyl-3,11-diphenyl-tridecan-7-one



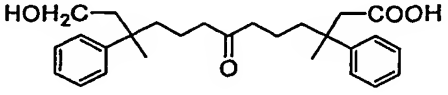
IIa-23

13-Hydroxy-3,11-dimethyl-7-oxo-3,11-diphenyl-tridecanoic acid



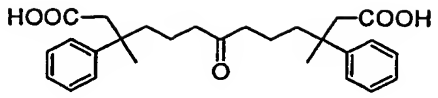
IIa-24

3,11-Dimethyl-7-oxo-3,11-diphenyl-tridecanedioic acid



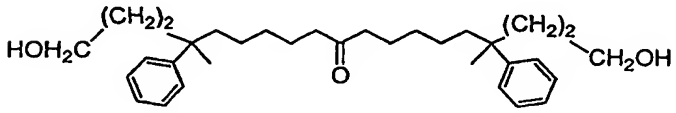
IIa-25

13-Hydroxy-3,11-dimethyl-7-oxo-3,11-diphenyl-tridecanoic acid



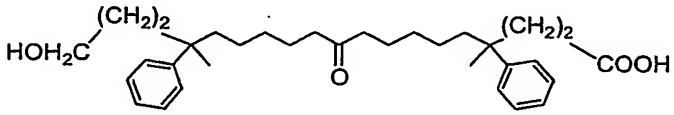
IIa-26

3,11-Dimethyl-7-oxo-3,11-diphenyl-tridecanedioic acid



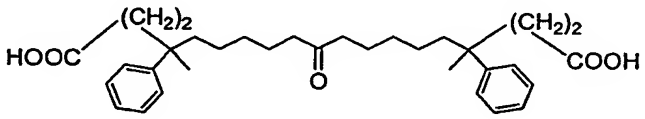
IIa-27

1,19-Dihydroxy-4,16-dimethyl-4,16-diphenyl-nonadecan-10-one



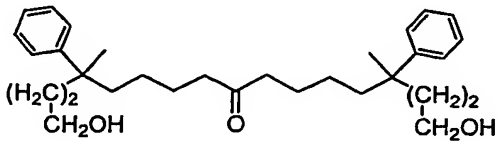
IIa-28

19-Hydroxy-4,16-dimethyl-10-oxo-4,16-diphenyl-nonadecanoic acid



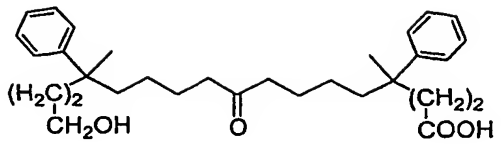
IIa-29

4,16-Dimethyl-10-oxo-4,16-diphenyl-nonadecanedioic acid



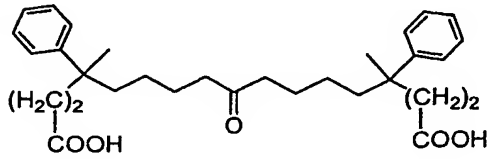
IIa-30

1,17-Dihydroxy-4,14-dimethyl-4,14-diphenyl-heptadecan-9-one



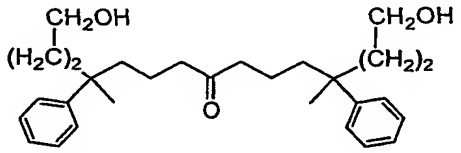
IIa-31

17-Hydroxy-4,14-dimethyl-9-oxo-4,14-diphenyl-heptadecanoic acid



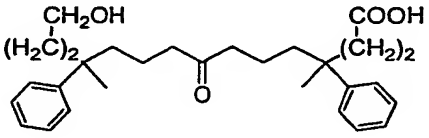
IIa-32

4,14-Dimethyl-9-oxo-4,14-diphenyl-heptadecanedioic acid



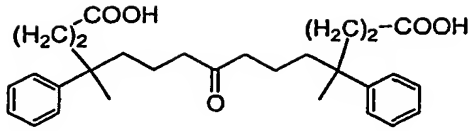
IIa-33

1,15-Dihydroxy-4,12-dimethyl-4,12-diphenyl-pentadecan-8-one



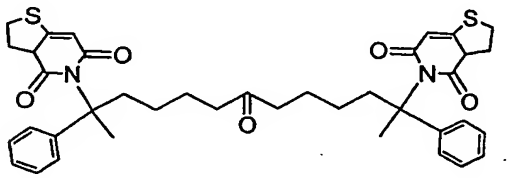
IIa-34

15-Hydroxy-4,12-dimethyl-8-oxo-4,12-diphenyl-pentadecanoic acid



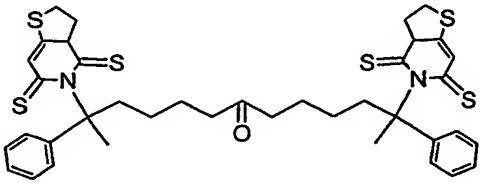
IIa-35

4,12-Dimethyl-8-oxo-4,12-diphenyl-pentadecanedioic acid



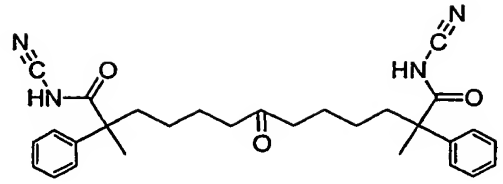
IIa-36

2,12-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,12-diphenyl-tridecan-7-one



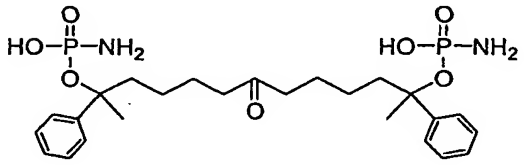
IIa-37

2,12-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,12-diphenyl-tridecan-7-one



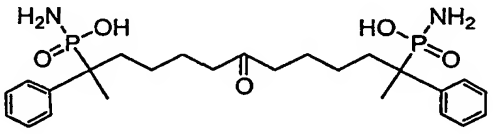
IIa-38

2,12-Dimethyl-2,12-diphenyl-7-oxo-tridecanedioic acid bis-cyanoamide



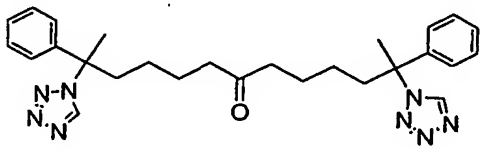
IIa-39

Phosphoramidic acid mono-[11-(amino-hydroxy-phosphoryloxy)-1-methyl-6-oxo-1,11-diphenyl-dodecyl] ester



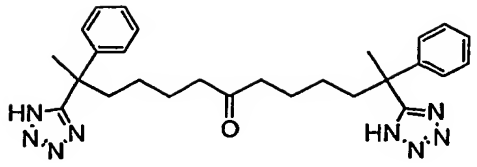
IIa-40

Phosphoramidic acid mono-[11(amino-hydroxy-phosphoryloxy)-1,11-dipehnyl-1-methyl-6-oxo-dodecyl] ester



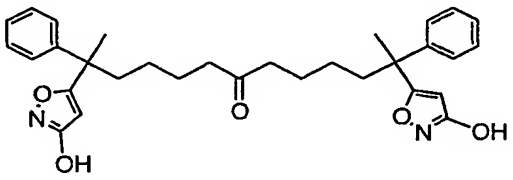
IIa-41

2,12-Diphenyl-2,12-bis-tetrazol-1-yl-tridecan-7-one



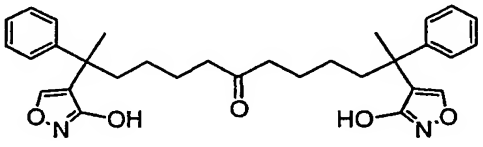
IIa-42

2,12-Diphenyl-2,12-bis-(1H-tetrazol-5-yl)-tridecan-7-one



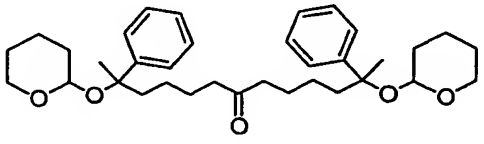
IIa-43

2,12-Bis-(3-hydroxy-isoxazol-5-yl)-2,12-diphenyl-tridecan-7-one



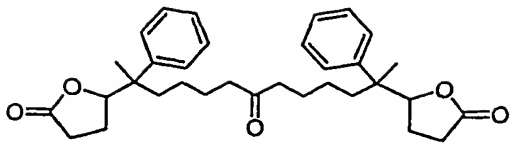
IIa-44

2,12-Bis-(3-hydroxy-isoxazol-4-yl)-2,12-diphenyl-tridecan-7-one



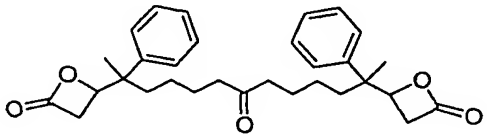
IIa-45

2,12-Diphenyl-2,12-bis-(tetrahydro-pyran-2-yloxy)-tridecan-7-one



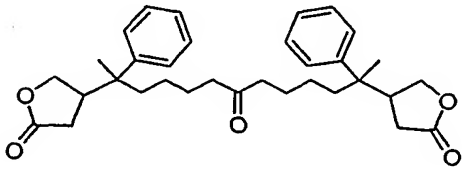
IIa-46

5-[11-(5-oxo-tetrahydro-furan-2-yl)-1,11-Diphenyl-1-methyl-6-oxo-dodecyl]-dihydro-furan-2-one



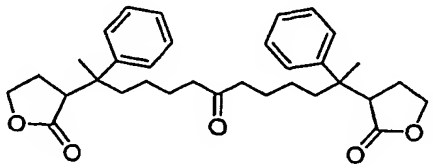
IIa-47

4-[11-(4-oxo-oxetan-2-yl)-1,11-diphenyl-1-methyl-6-oxo-dodecyl]-oxetan-2-one



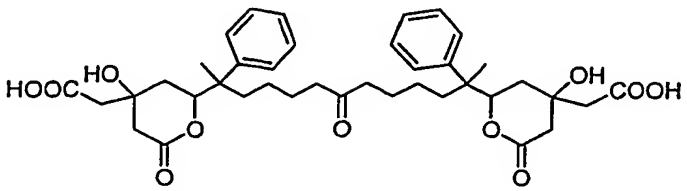
IIa-48

4-[11-(5-oxo-tetrahydro-furan-2-yl)-1,11-Diphenyl-1-methyl-6-oxo-dodecyl]-dihydro-furan-2-one



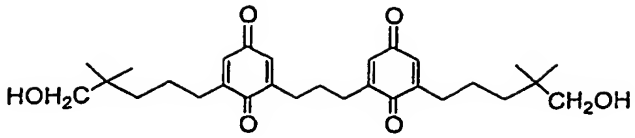
IIa-49

3-[11-(5-oxo-tetrahydro-furan-2-yl)-1,11-Diphenyl-1-methyl-6-oxo-dodecyl]-dihydro-furan-2-one



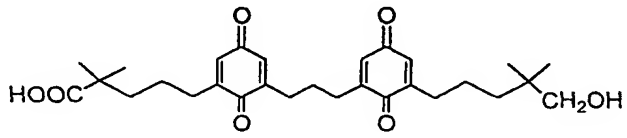
IIa-50

{2-[11-(4-Carboxymethyl-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-1-methyl-6-oxo-1,11-diphenyl-dodecyl]-4-hydroxy-6-oxo-tetrahydro-pyran-4-yl}-acetic acid



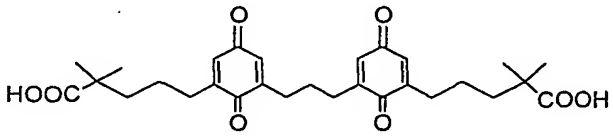
III-1

5-(6-{3-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-propyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentan-1-ol



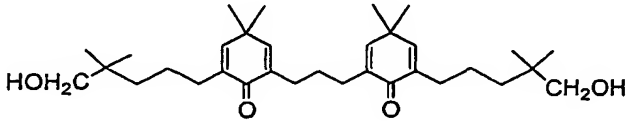
III-2

5-(6-{3-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-propyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid



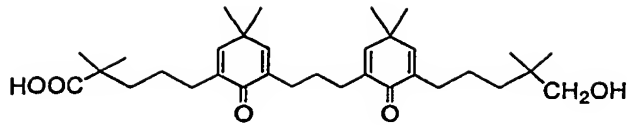
III-3

5-(6-{3-[6-(4-Carboxy-4-methyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-propyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid



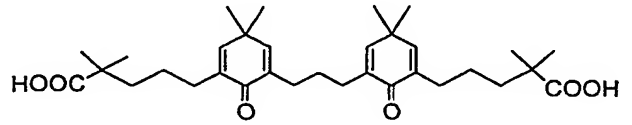
III-4

5-(6-{3-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-propyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentan-1-ol



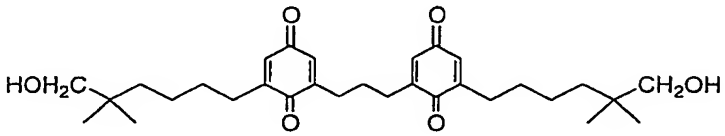
III-5

5-(6-{3-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-propyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid



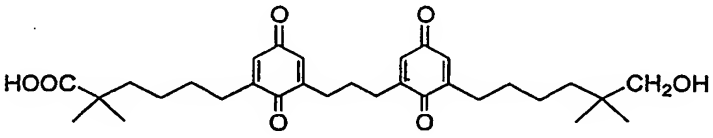
III-6

5-(6-{3-[6-(4-Carboxy-4-methyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-propyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid



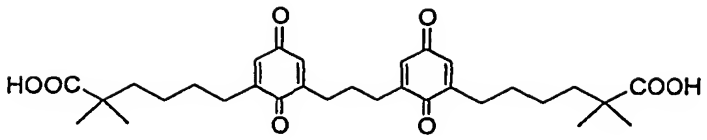
III-7

6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-propyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexan-1-ol



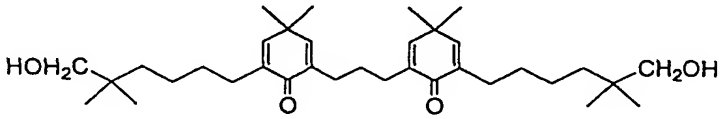
III-8

6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-propyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid



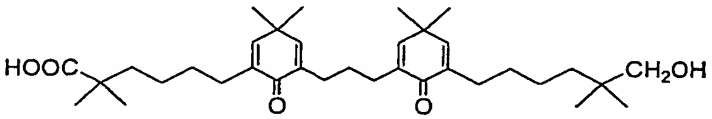
III-9

6-(6-{3-[6-(5-Carboxy-5-methyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-propyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid



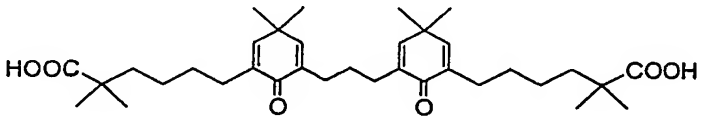
III-10

6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-propyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexan-1-ol



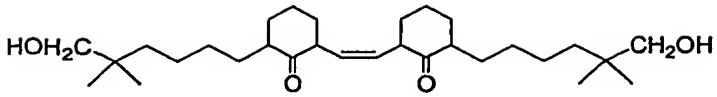
III-11

6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-propyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid



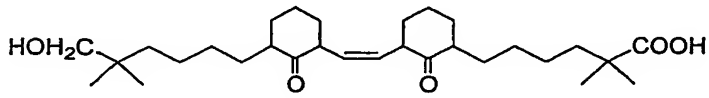
III-12

6-(6-{3-[6-(5-Carboxy-5-methyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-propyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid



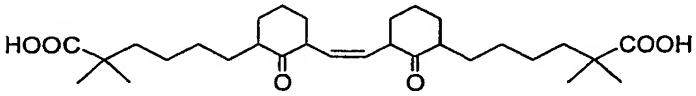
III-13

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-vinyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexan-1-ol



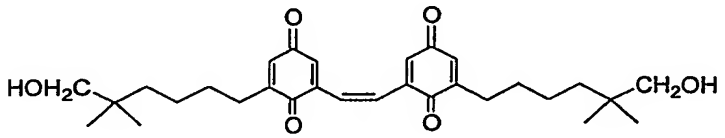
III-14

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-vinyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexanoic acid



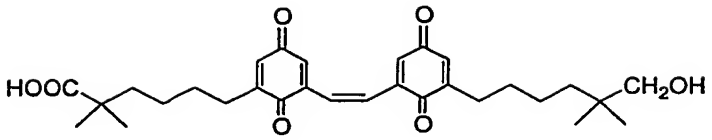
III-15

6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-1-oxo-cyclohexan-2-yl]-vinyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexanoic acid



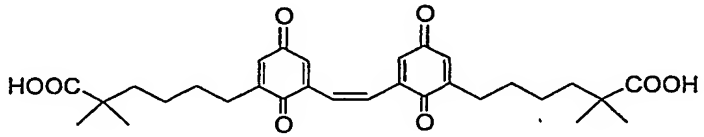
III-16

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-vinyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexan-1-ol



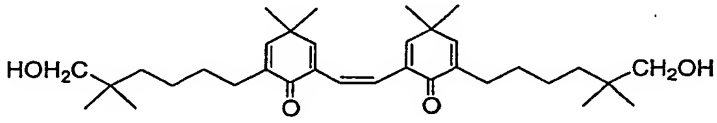
III-17

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-vinyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid



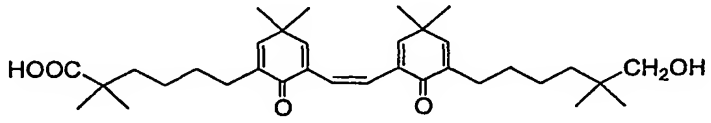
III-18

6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-vinyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid



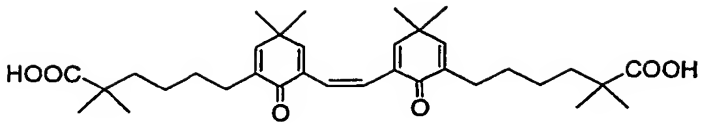
III-19

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-vinyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexan-1-ol



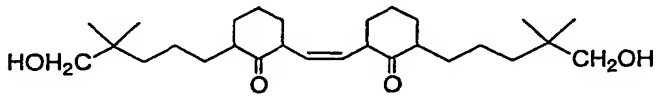
III-20

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-vinyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid



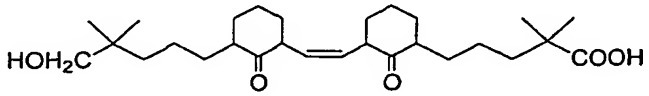
III-21

6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-vinyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid



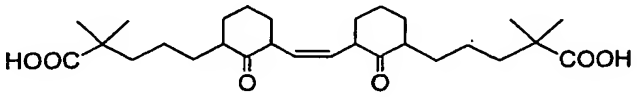
III-22

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclohexan-2-yl]-vinyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentan-1-ol



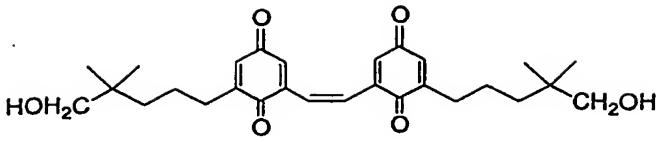
III-23

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclohexan-2-yl]-vinyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentanoic acid



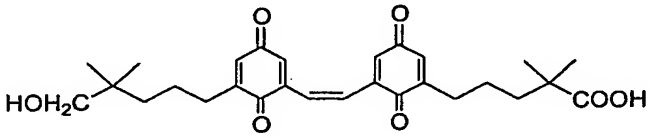
III-24

5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclohexan-2-yl]-vinyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentanoic acid



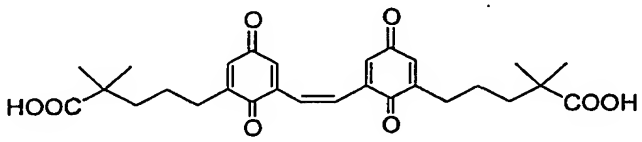
III-25

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-vinyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentan-1-ol



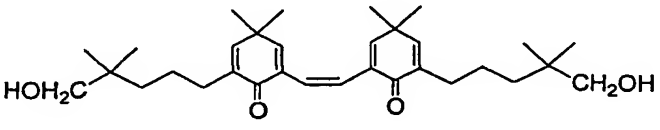
III-26

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-vinyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid



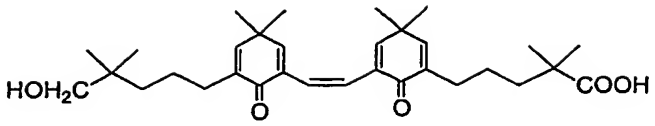
III-27

5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-vinyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid



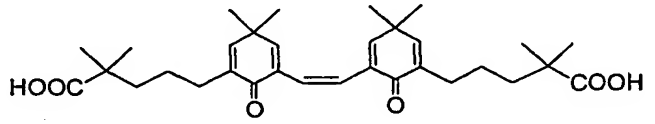
III-28

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-vinyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentan-1-ol



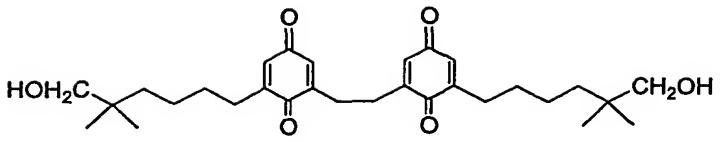
III-29

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-vinyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid



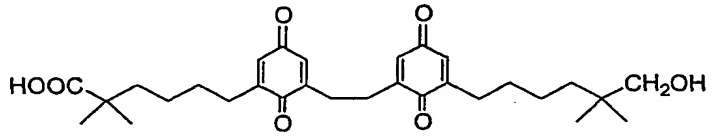
III-30

5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-vinyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid



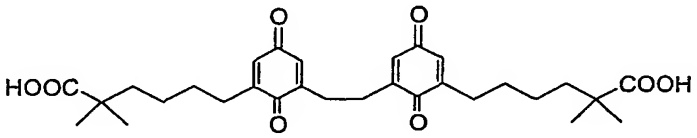
III-31

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-ethyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexan-1-ol



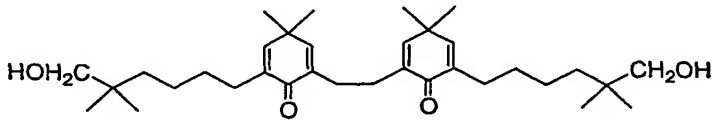
III-32

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-ethyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid



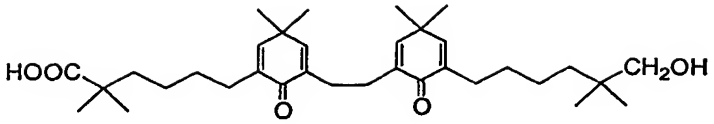
III-33

6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-ethyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid



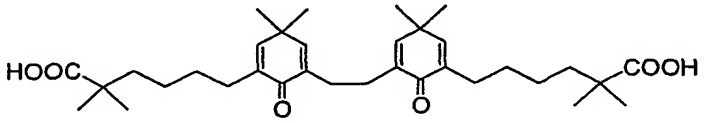
III-34

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-ethyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexan-1-ol



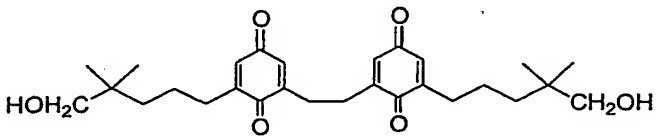
III-35

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-ethyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid



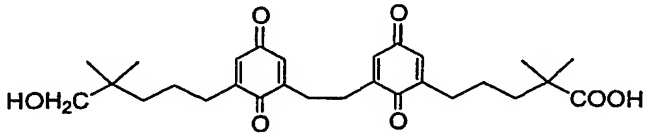
III-36

6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-ethyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid



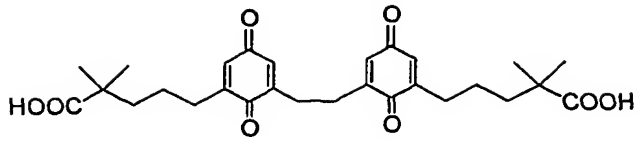
III-37

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-ethyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentan-1-ol



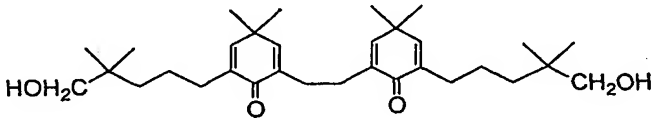
III-38

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-ethyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid



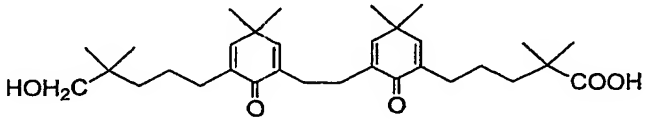
III-39

5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-ethyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid



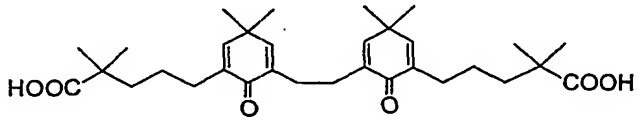
III-40

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-ethyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentan-1-ol



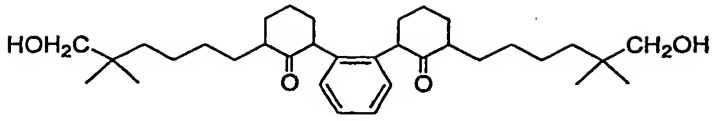
III-41

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-ethyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid



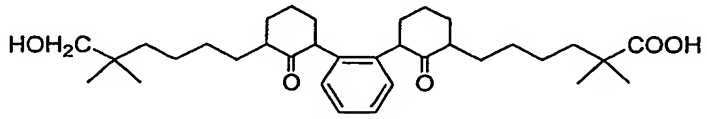
III-42

5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-ethyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid



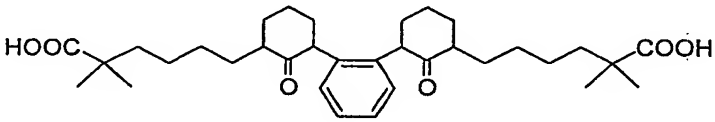
III-43

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-phenyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexan-1-ol



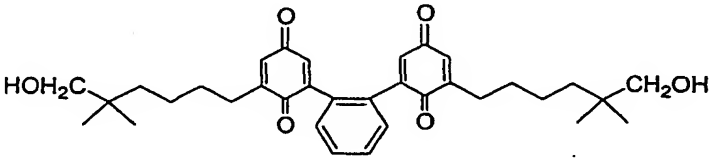
III-44

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-phenyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexanoic acid



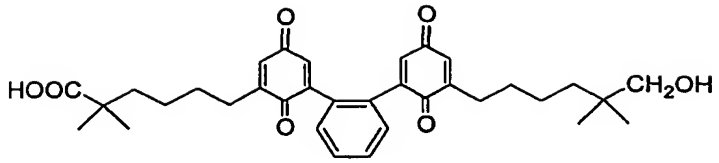
III-45

6-(6-{2-[6-(6-Carboxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-phenyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexanoic acid



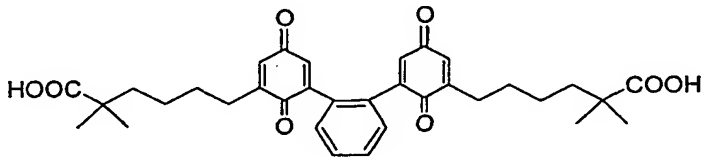
III-46

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-phenyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexan-1-ol



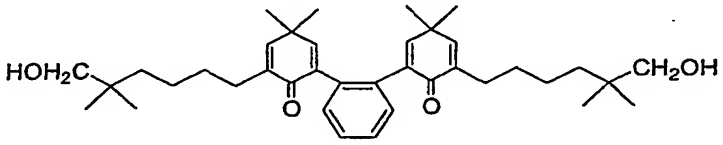
III-47

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-phenyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid



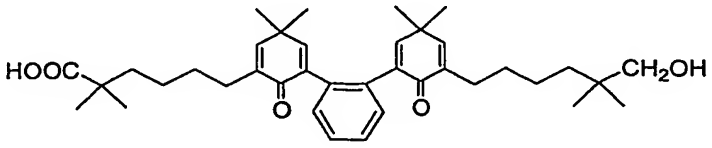
III-48

6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-phenyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid



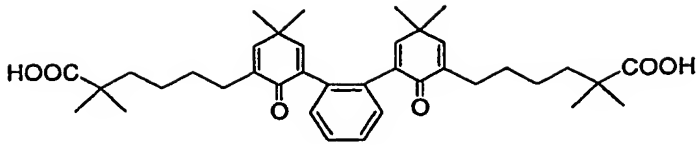
III-49

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-phenyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexan-1-ol



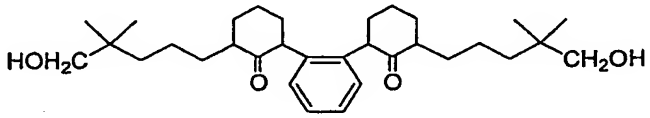
III-50

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-phenyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid



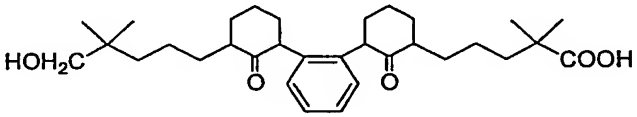
III-51

6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-phenyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid



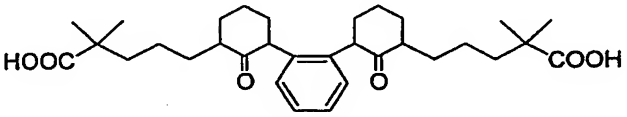
III-52

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclohexan-2-yl]-phenyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentan-1-ol



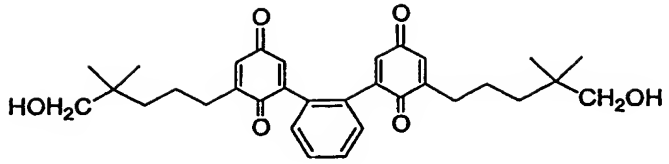
III-53

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclohexan-2-yl]-phenyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentanoic acid



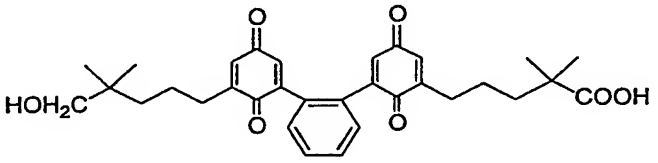
III-54

5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclohexan-2-yl]-phenyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentanoic acid



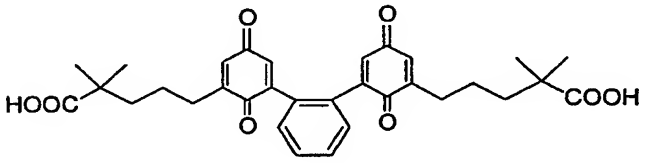
III-55

5-(6-{2-[6-(5-Hydroxy-4-methyl-pentyl)-1,4-dioxo-cyclohex-2-yl]-phenyl}-1,4-dioxo-cyclohex-2-yl)-2,2-dimethyl-pentan-1-ol



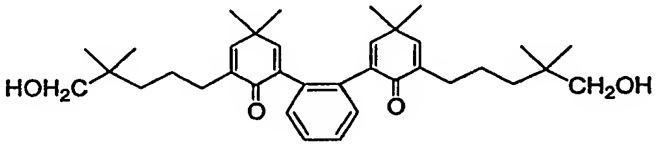
III-56

5-(6-{2-[6-(5-Hydroxy-4-methyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-phenyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid



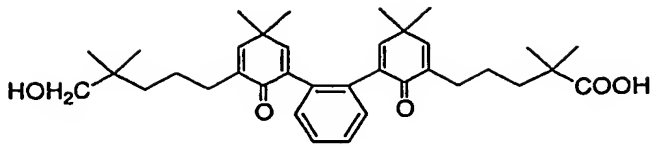
III-57

5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-phenyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid



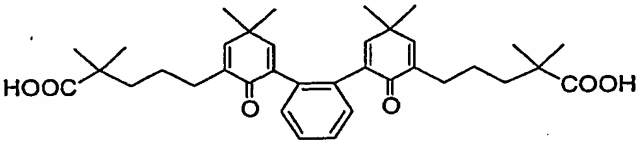
III-58

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-phenyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentan-1-ol



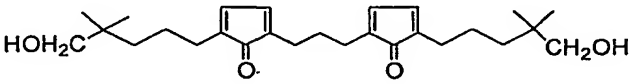
III-59

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-phenyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid



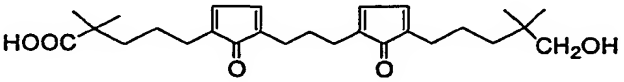
III-60

5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-phenyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid



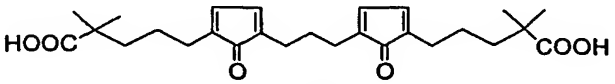
III-61

5-(5-{3-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentadien-2-yl]-propyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentan-1-ol



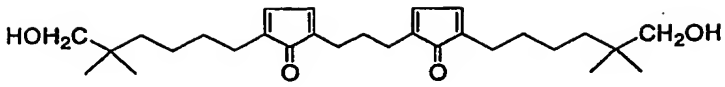
III-62

5-(5-{3-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentadien-2-yl]-propyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentanoic acid



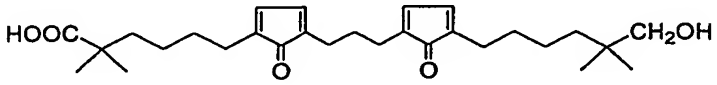
III-63

5-(5-{3-[5-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclopentadien-2-yl]-propyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentanoic acid



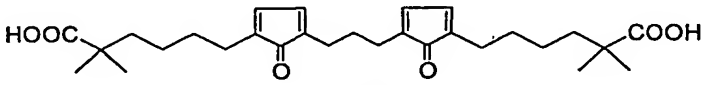
III-64

6-(5-{3-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentadien-2-yl]-propyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexan-1-ol



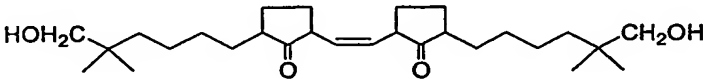
III-65

6-(5-{3-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentadien-2-yl]-propyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexanoic acid



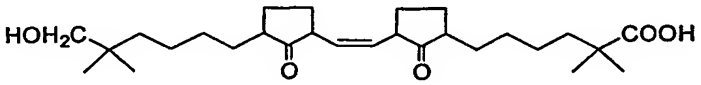
III-66

6-(5-{3-[5-(5-Carboxy-5-methyl-hexyl)-1-oxo-cyclopentadien-2-yl]-propyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexanoic acid



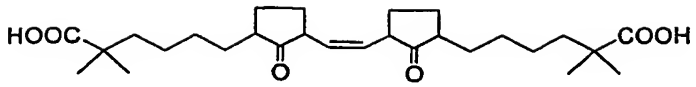
III-67

6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-hexan-1-ol



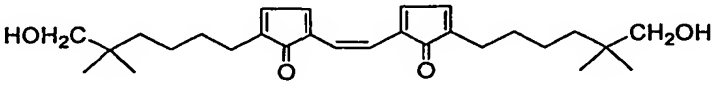
III-68

6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-hexanoic acid



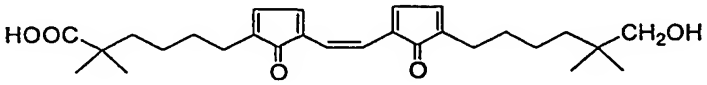
III-69

6-(5-{2-[5-(5-Carboxy-5-methyl-hexyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-hexanoic acid



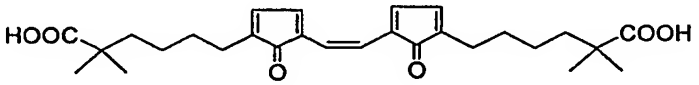
III-70

6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexan-1-ol



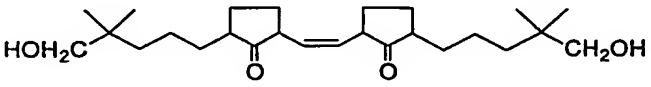
III-71

6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexanoic acid



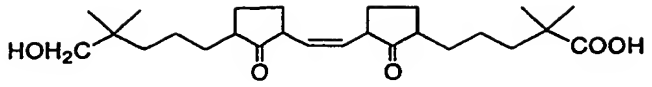
III-72

6-(5-{2-[5-(5-Carboxy-5-methyl-hexyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexanoic acid



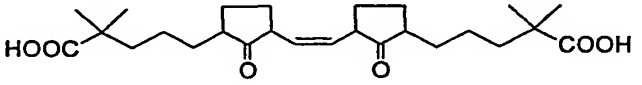
III-73

5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-pentan-1-ol



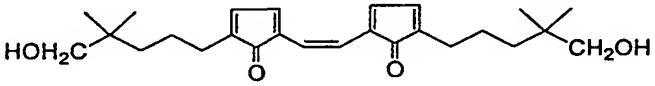
III-74

5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-pentanoic acid



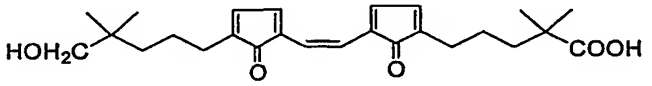
III-75

5-(5-{2-[5-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-pentanoic acid



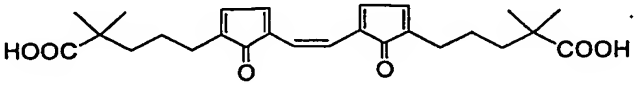
III-76

5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentan-1-ol



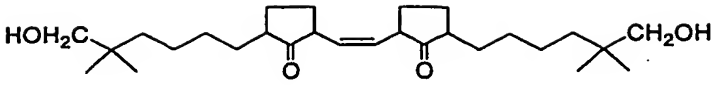
III-77

5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentanoic acid



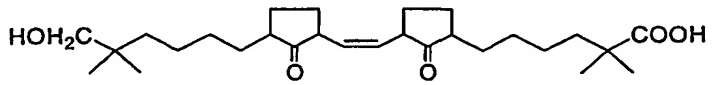
III-78

5-(5-{2-[5-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentanoic acid



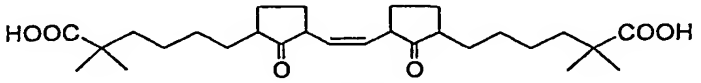
III-79

6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-hexan-1-ol



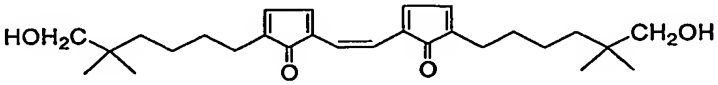
III-80

6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-hexanoic acid



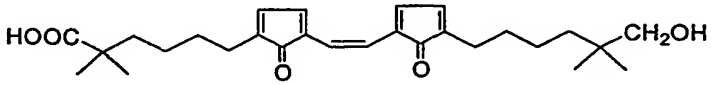
III-81

6-(5-{2-[5-(5-Carboxy-5-methyl-hexyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-hexanoic acid



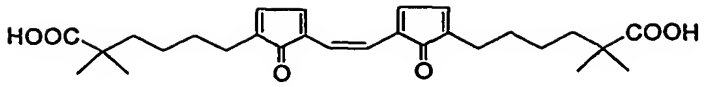
III-82

6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexan-1-ol



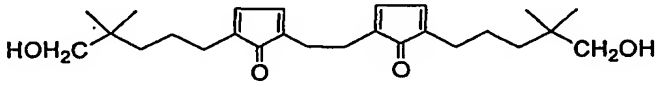
III-83

6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexanoic acid



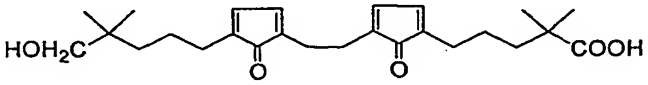
III-84

6-(5-{2-[5-(5-Carboxy-5-methyl-hexyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexanoic acid



III-85

5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentadien-2-yl]-ethyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentan-1-ol

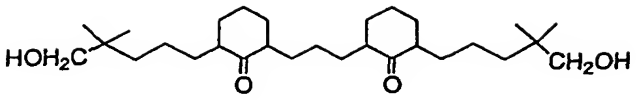


III-86

5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentadien-2-yl]-ethyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentanoic acid

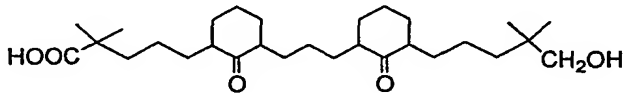
III-87

5-(5-{2-[5-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclopentadien-2-yl]-ethyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentanoic acid



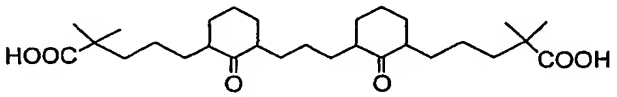
IIIa-1

5-(6-{3-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclohexan-2-yl]-propyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentan-1-ol



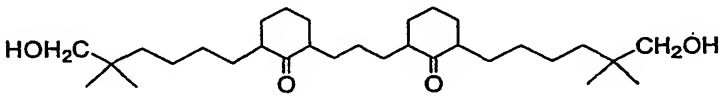
IIIa-2

5-(6-{3-[6-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclohexan-2-yl]-propyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentanoic acid



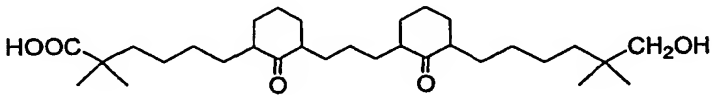
IIIa-3

5-(6-{3-[6-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclohexan-2-yl]-propyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentanoic acid



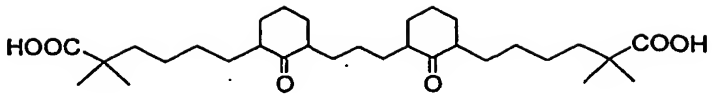
IIIa-4

6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-propyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexan-1-ol



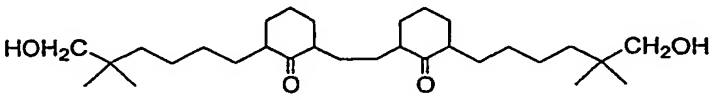
IIIa-5

6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-propyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexanoic acid



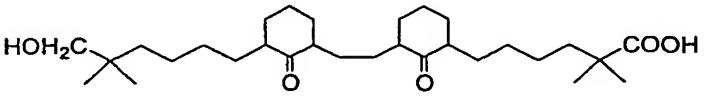
IIIa-6

6-(6-{3-[6-(5-Carboxy-5-methyl-hexyl)-1-oxo-cyclohexan-2-yl]-propyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexanoic acid



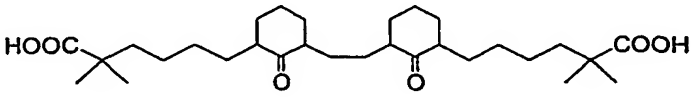
IIIa-7

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-ethyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexan-1-ol



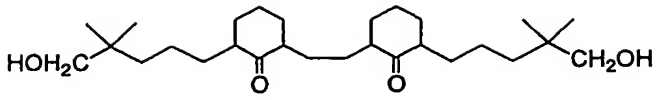
IIIa-8

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-ethyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexanoic acid



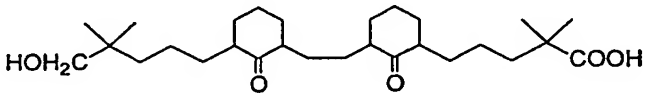
IIIa-9

6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-1-oxo-cyclohexan-2-yl]-ethyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexanoic acid



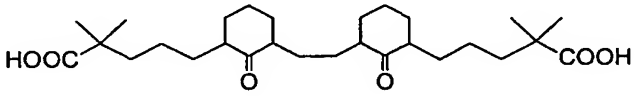
IIIa-10

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclohexan-2-yl]-ethyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentan-1-ol



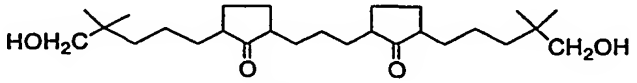
IIIa-11

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclohexan-2-yl]-ethyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentanoic acid



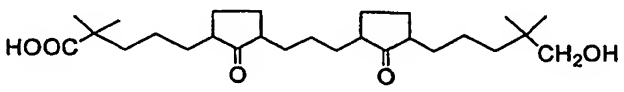
IIIa-12

5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclohexan-2-yl]-ethyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentanoic acid



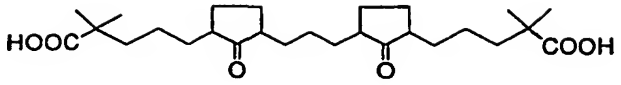
IIIa-13

5-(5-{3-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentan-2-yl]-propyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-pentan-1-ol



IIIa-14

5-(5-{3-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentan-2-yl]-propyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-pentanoic acid



IIIa-15

5-(5-{3-[5-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclopentan-2-yl]-propyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-pentanoic acid

4.1. Definitions and Abbreviations

Apo(a): apolipoprotein(a)

Apo A-I: apolipoprotein A-I

Apo B: apolipoprotein B

Apo E: apolipoprotein E

FH: Familial hypercholesterolemia

FCH: Familial combined hyperlipidemia

GDM: Gestational diabetes mellitus

HDL: High density lipoprotein

IDL: Intermediate density lipoprotein

IDDM: Insulin dependent diabetes mellitus

LDH: Lactate dehdyrogenase

LDL: Low density lipoprotein

Lp(a): Lipoprotein (a)

MODY: Maturity onset diabetes of the young

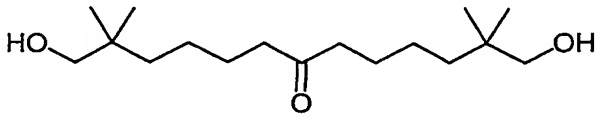
NIDDM: Non-insulin dependent diabetes mellitus

PPAR: Peroxisome proliferator activated receptor

RXR: Retinoid X receptor

VLDL: Very low density lipoprotein

The term "compound A" means the compound 1,13-dihydroxy-2,2,12,12-tetramethyl-tridecan-7-one having the structure:



Compound A

1,13-Dihydroxy-2,2,12,12-tetramethyl-tridecan-7-one

The compounds of the invention can contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric isomers), enantiomers, or diastereomers. According to the invention, the chemical structures depicted herein, and therefore the compounds of the invention, encompass all of the corresponding compound's enantiomers and stereoisomers, that is,

both the stereomerically pure form (*e.g.*, geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures.

A compound of the invention is considered optically active or enantiomerically pure (*i.e.*, substantially the R-form or substantially the S-form) with respect to a chiral center when the compound is about 90% ee (enantiomeric excess) or greater, preferably, equal to or greater than 95% ee with respect to a particular chiral center. A compound of the invention is considered to be in enantiomerically-enriched form when the compound has an enantiomeric excess of greater than about 80% ee with respect to a particular chiral center. A compound of the invention is considered diastereomerically pure with respect to multiple chiral centers when the compound is about 90% de (diastereomeric excess) or greater, preferably, equal to or greater than 95% de with respect to a particular chiral center. A compound of the invention is considered to be in diastereomerically-enriched form when the compound has an diastereomeric excess of greater than about 80% de with respect to a particular chiral center. As used herein, a racemic mixture means about 50% of one enantiomer and about 50% of is corresponding enantiomer relative to all chiral centers in the molecule. Thus, the invention encompasses all enantiomerically-pure, enantiomerically-enriched, diastereomerically pure, diastereomerically enriched, and racemic mixtures of compounds of Formulas **I** through **III**.

Enantiomeric and diastereomeric mixtures can be resolved into their component enantiomers or stereoisomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and diastereomers can also be obtained from diastereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

The compounds of the invention are defined herein by their chemical structures and/or chemical names. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound's identity.

When administered to a patient, *e.g.*, to an animal for veterinary use or for improvement of livestock, or to a human for clinical use, the compounds of the invention are administered in isolated form or as the isolated form in a pharmaceutical composition. As used herein, "isolated" means that the compounds of the invention are separated from other components of either (a) a natural source, such as a plant or cell, preferably bacterial culture, or (b) a synthetic organic chemical reaction mixture. Preferably, via conventional

techniques, the compounds of the invention are purified. As used herein, "purified" means that when isolated, the isolate contains at least 95%, preferably at least 98%, of a single ether compound of the invention by weight of the isolate.

The phrase "pharmaceutically acceptable salt(s)," as used herein includes, but are not limited to, salts of acidic or basic groups that may be present in the compounds of the invention. Compounds that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, including but not limited to sulfuric, citric, maleic, acetic, oxalic, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds of the invention that include an amino moiety also can form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds of the invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium lithium, zinc, potassium, and iron salts.

As used herein, the term "solvate" means a compound of the invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of a solvent bound by non-covalent intermolecular forces. Preferred solvents are volatile, non-toxic, and/or acceptable for administration to humans in trace amounts.

As used herein, the term "hydrate" means a compound of the invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

As used herein, the term "clathrate" means a compound of the invention or a salt thereof in the form of a crystal lattice that contains spaces (*e.g.*, channels) that have a guest molecule (*e.g.*, a solvent or water) trapped within.

"Altering lipid metabolism" indicates an observable (measurable) change in at least one aspect of lipid metabolism, including but not limited to total blood lipid content, blood HDL cholesterol, blood LDL cholesterol, blood VLDL cholesterol, blood triglyceride, blood Lp(a), blood apo A-I, blood apo E and blood non-esterified fatty acids.

"Altering glucose metabolism" indicates an observable (measurable) change in at least one aspect of glucose metabolism, including but not limited to total blood glucose content, blood insulin, the blood insulin to blood glucose ratio, insulin sensitivity, and oxygen consumption.

As used herein, the term "alkyl group" means a saturated, monovalent unbranched or branched hydrocarbon chain. Examples of alkyl groups include, but are not limited to, (C_1–C_6)alkyl groups, such as methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, *t*–butyl, pentyl, isopentyl, neopentyl, and hexyl, and longer alkyl groups, such as heptyl, and octyl. An alkyl group can be unsubstituted or substituted with one or two suitable substituents.

An "alkenyl group" means a monovalent unbranched or branched hydrocarbon chain having one or more double bonds therein. The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkenyl groups include, but are not limited to (C_2–C_6)alkenyl groups, such as vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl. An alkenyl group can be unsubstituted or substituted with one or two suitable substituents.

An "alkynyl group" means monovalent unbranched or branched hydrocarbon chain having one or more triple bonds therein. The triple bond of an alkynyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkynyl groups include, but are not limited to, (C_2–C_6)alkynyl groups, such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butynyl, 4-propyl-2-pentynyl, and 4-butyl-2-hexynyl. An alkynyl group can be unsubstituted or substituted with one or two suitable substituents.

An "aryl group" means a monocyclic or polycyclic-aromatic radical comprising carbon and hydrogen atoms. Examples of suitable aryl groups include, but are not limited to, phenyl, tolyl, anthacenyl, fluorenyl, indenyl, azulenyl, and naphthyl, as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl. An aryl group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the aryl group is a monocyclic ring, wherein the ring comprises 6 carbon atoms, referred to herein as "(C_6)aryl".

A "heteroaryl group" means a monocyclic- or polycyclic aromatic ring comprising carbon atoms, hydrogen atoms, and one or more heteroatoms, preferably 1 to 3 heteroatoms,

independently selected from nitrogen, oxygen, and sulfur. Illustrative examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrimidinyl, pyrazyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3)- and (1,2,4)-triazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, furyl, thiophenyl, isoxazolyl, thiazolyl, furyl, phenyl, isoxazolyl, and oxazolyl. A heteroaryl group can be unsubstituted or substituted with one or two suitable substituents. Preferably, a heteroaryl group is a monocyclic ring, wherein the ring comprises 2 to 5 carbon atoms and 1 to 3 heteroatoms, referred to herein as "(C_2–C_5)heteroaryl".

A "cycloalkyl group" means a monocyclic or polycyclic saturated ring comprising carbon and hydrogen atoms and having no carbon-carbon multiple bonds. Examples of cycloalkyl groups include, but are not limited to, (C_3–C_7)cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl group can be unsubstituted or substituted by one or two suitable substituents. Preferably, the cycloalkyl group is a monocyclic ring or bicyclic ring.

A "heterocycloalkyl group" means a monocyclic or polycyclic ring comprising carbon and hydrogen atoms and at least one heteroatom, preferably, 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and having no unsaturation. Examples of heterocycloalkyl groups include pyrrolidinyl, pyrrolidino, piperidinyl, piperidino, piperazinyl, piperazino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, and pyranyl. A heterocycloalkyl group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the heterocycloalkyl group is a monocyclic or bicyclic ring, more preferably, a monocyclic ring, wherein the ring comprises from 3 to 6 carbon atoms and form 1 to 3 heteroatoms, referred to herein as (C_1–C_6)heterocycloalkyl.

As used herein a "heterocyclic radical" or "heterocyclic ring" means a heterocycloalkyl group or a heteroaryl group.

The term "alkoxy group"means an –O–alkyl group, wherein alkyl is as defined above. An alkoxy group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the alkyl chain of an alkyloxy group is from 1 to 6 carbon atoms in length, referred to herein as "(C_1–C_6)alkoxy".

The term "aryloxy group" means an –O–aryl group, wherein aryl is as defined above. An aryloxy group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the aryl ring of an aryloxy group is a monocyclic ring, wherein the ring comprises 6 carbon atoms, referred to herein as "(C_6)aryloxy".

The term "benzyl" means –CH_2–phenyl.

The term "phenyl" means $-C_6H_5$. A phenyl group can be unsubstituted or substituted with one or two suitable substituents.

A "hydrocarbyl" group means a monovalent group selected from (C_1-C_8)alkyl, (C_2-C_8)alkenyl, and (C_2-C_8)alkynyl, optionally substituted with one or two suitable substituents. Preferably, the hydrocarbon chain of a hydrocarbyl group is from 1 to 6 carbon atoms in length, referred to herein as "(C_1-C_6)hydrocarbyl".

A "carbonyl" group is a divalent group of the formula –C(O)–.

An "alkoxycarbonyl" group means a monovalent group of the formula –C(O)–alkoxy. Preferably, the hydrocarbon chain of an alkoxycarbonyl group is from 1 to 8 carbon atoms in length, referred to herein as a "lower alkoxycarbonyl" group.

A "carbamoyl" group means the radical $-C(O)N(R')_2$, wherein R' is chosen from the group consisting of hydrogen, alkyl, and aryl.

As used herein, "halogen" means fluorine, chlorine, bromine, or iodine. Correspondingly, the meaning of the terms "halo" and "Hal"encompass fluoro, chloro, bromo, and iodo.

As used herein, a "suitable substituent" means a group that does not nullify the synthetic or pharmaceutical utility of the compounds of the invention or the intermediates useful for preparing them. Examples of suitable substituents include, but are not limited to: (C_1-C_8)alkyl; (C_1-C_8)alkenyl; (C_1-C_8)alkynyl; (C_6)aryl; (C_2-C_5)heteroaryl; (C_3-C_7)cycloalkyl; (C_1-C_8)alkoxy; (C_6)aryloxy; –CN; –OH; oxo; halo, $-CO_2H$; $-NH_2$; $-NH((C_1-C_8)alkyl)$; $-N((C_1-C_8)alkyl)_2$; $-NH((C_6)aryl)$; $-N((C_6)aryl)_2$; –CHO; $-CO((C_1-C_8)alkyl)$; $-CO((C_6)aryl)$; $-CO_2((C_1-C_8)alkyl)$; and $-CO_2((C_6)aryl)$. One of skill in the art can readily choose a suitable substituent based on the stability and pharmacological and synthetic activity of the compound of the invention.

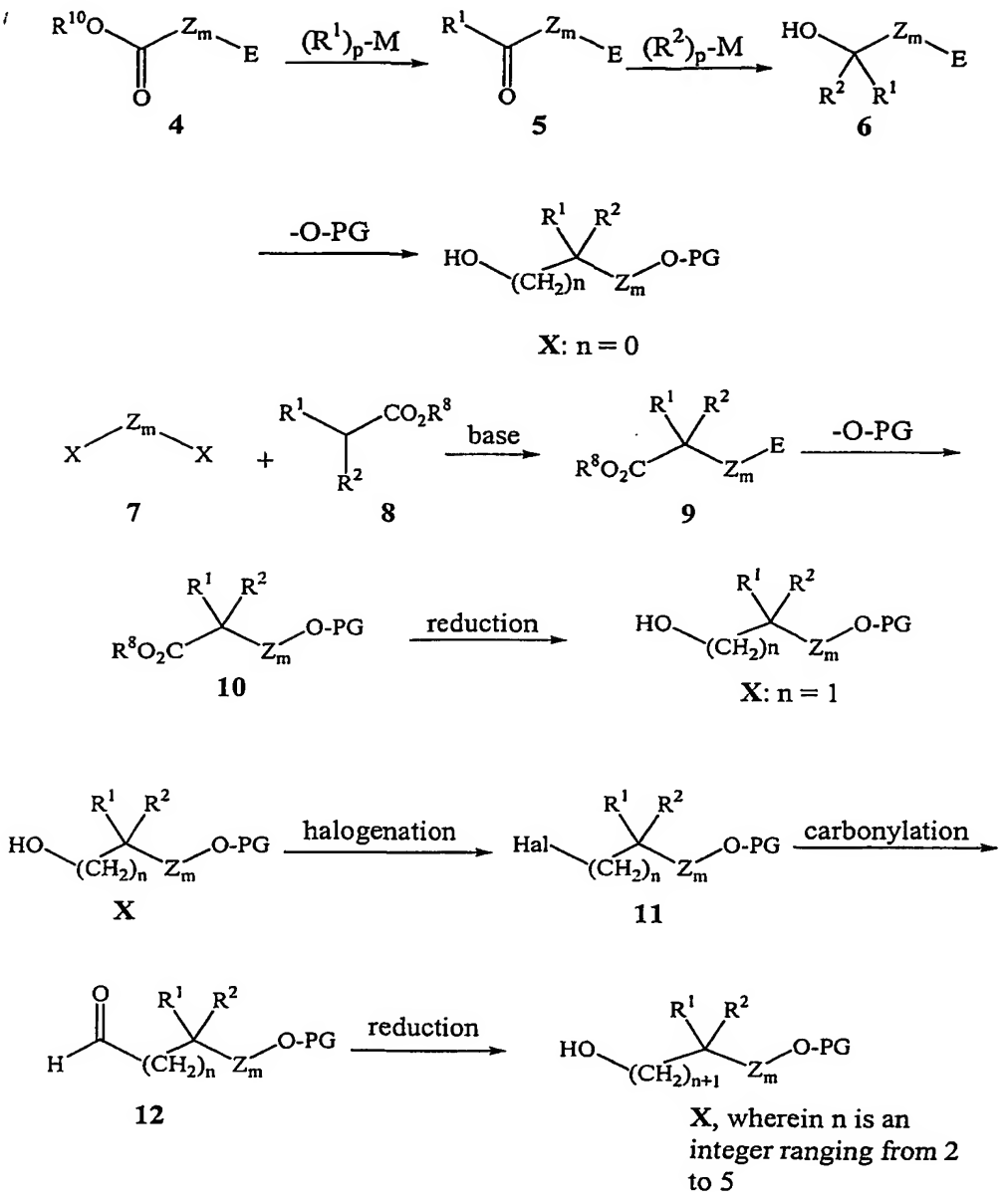
4.2. Synthesis of the Compounds of the Invention

The compounds of the invention can be obtained via the synthetic methodology illustrated in Schemes 1-13. Starting materials useful for preparing the compounds of the invention and intermediates thereof, are commercially available or can be prepared from commercially available materials using known synthetic methods and reagents.

Scheme 1 illustrates the synthesis of mono-protected diols of the formula **X**, wherein n is an integer ranging from 0 to 4 and R^1 and R^2 are as defined above, and E is a leaving group as defined below. Scheme 1 first outlines the synthesis of mono-protected diols **X**, wherein n is 0, where esters **4** are successively reacted with a first $((R^1)_p–M)$ then a second $((R^2)_p–M)$ organometallic reagent providing ketones **5** and alcohols **6**, respectively. M is a

metal group and p is the metal's valency value (*e.g.*, the valency of Li is 1 and that of Zn is 2). Suitable metals include, but are not limited to, Zn, Na, Li, and –Mg–Hal, wherein Hal is a halide selected from iodo, bromo, or chloro. Preferably, M is –Mg–Hal, in which case the organometallic reagents, $(R^1)_p$–Mg–Hal and $(R^2)_p$–Mg–Hal, are known in the art as a Grignard reagents. Esters **4** are available commercially (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or can be prepared by well-known synthetic methods, for example, *via* esterification of the appropriate 5-halovaleric acid (commercially available, *e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin). Both $(R^1)_p$–M and $(R^2)_p$–M are available commercially (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or can be prepared by well-known methods (see *e.g.*, Kharasch *et al.*, *Grignard Reactions of Non-Metallic Substances*; Prentice-Hall, Englewood Cliffs, NJ, pp. 138-528 (1954) and Hartley; Patai, *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley: New York, pp. 159-306 and pp. 162-175 (1989), both citations are hereby expressly incorporated herein by reference).

Scheme 1: Synthesis of Compounds of Formula X



The reaction of a first ($(R^1)_p$–M) then a second ($(R^2)_p$–M) organometallic reagent with esters **4** can be performed using the general procedures referenced in March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 920-929 and Eicher, Patai, *The Chemistry of the Carbonyl Group*, pt. 1, pp. 621-693; Wiley: New York, (1966), hereby expressly incorporated herein by reference. For example, the

synthetic procedure described in Comins *et al.*, 1981,*Tetrahedron Lett.* 22:1085, hereby expressly incorporated herein by reference, can be used. As one example, the reaction can be performed by adding an organic solution of $(R^1)_p$–M (about 0.5 to about 1 equivalents) to a stirred, cooled (about 0°C to about –80°C) solution comprising esters **4**, under an inert atmosphere (*e.g.*, nitrogen) to give a reaction mixture comprising ketones **5**. Preferably, $(R^1)_p$–M is added at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. The progress of the reaction can be followed by using an appropriate analytical method, such as thin-layer chromatography or high-performance-liquid chromatography. Next, an organic solution of $(R^2)_p$–M (about 0.5 to about 1 equivalent) is added to the reaction mixture comprising ketones **5** in the same manner used to add $(R^1)_p$–M. After the reaction providing alcohols **6** is substantially complete, the reaction mixture can be quenched and the product can be isolated by workup. Suitable solvents for obtaining alcohols **6** include, but are not limited to, dichloromethane, diethyl ether, tetrahydrofuran, benzene, toluene, xylene, hydrocarbon solvents (*e.g.*, pentane, hexane, and heptane), and mixtures thereof. Preferably, the organic solvent is diethyl ether or tetrahydrofuran. Next, alcohols **6** are converted to mono-protected diols **X**, wherein n is 0, using the well-known Williamson ether synthesis. This involves reacting alcohols **6** with $^-$O–PG, wherein –PG is a hydroxy-protecting group. For a general discussion of the Williamson ether synthesis, *See* March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 386-387, and for a list of procedures and reagents useful in the Williamson ether synthesis, *See, for example,* Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, pp. 446-448, both of which references are incorporated herein by reference. As used herein, a "hydroxy-protecting group" means a group that is reversibly attached to a hydroxy moiety that renders the hydroxy moiety unreactive during a subsequent reaction(s) and that can be selectively cleaved to regenerate the hydroxy moiety once its protecting purpose has been served. Examples of hydroxy-protecting groups are found in Greene, T.W., *Protective Groups in Organic Synthesis*, 3rd edition 17-237 (1999), hereby expressly incorporated herein by reference. Preferably, the hydroxy-protecting group is stable in a basic reaction medium, but can be cleaved by acid. Examples of suitable base-stable acid-labile hydroxy-protecting groups suitable for use with the invention include, but are not limited to, ethers, such as methyl, methoxy methyl, methylthiomethyl, methoxyethoxymethyl, *bis*(2-chloroethoxy)methyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahyrofuranyl, tetrahydrothiofuranyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, *t*-butyl, allyl, benzyl, *o*-nitrobenzyl, triphenylmethyl, α-naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl,

9-(9-phenyl-10-oxo)anthranyl, trimethylsilyl, isopropyldimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, and triisopropylsilyl; and esters, such as pivaloate, adamantoate, and 2,4,6-trimethylbenzoate. Ethers are preferred, particularly straight chain ethers, such as methyl ether, methoxymethyl ether, methylthiomethyl ether, methoxyethoxymethyl ether, *bis*(2-chloroethoxy)methyl ether. Preferably –PG is methoxymethyl (CH_3OCH_2–). Reaction of alcohols **6** with $^-$O–PG under the conditions of the Williamson ether synthesis involves adding a base to a stirred organic solution comprising HO–PG (*e.g.*, methoxymethanol), maintained at a constant temperature within the range of about 0°C to about 80°C, preferably at about room temperature. Preferably, the base is added at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. The base can be added as an organic solution or in undiluted form. Preferably, the base will have a base strength sufficient to deprotonate a proton, wherein the proton has a pK_a of greater than about 15, preferably greater than about 20. As is well known in the art, the pK_a is a measure of the acidity of an acid H–A, according to the equation $pK_a = -\log K_a$, wherein K_a is the equilibrium constant for the proton transfer. The acidity of an acid H–A is proportional to the stability of its conjugate base $^-$A. For tables listing pK_a values for various organic acids and a discussion on pK_a measurement, see March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 248-272, incorporated herein by reference. Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*–butyllithium, *tert*–butyllithium, *sec*–butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium hydride and potassium hydride. The preferred base is lithium diisopropylamide. Solvents suitable for reacting alcohols **6** with –OPG include, but are not limited, to dimethyl sulfoxide, dichloromethane, ethers, and mixtures thereof, preferably tetrahydrofuran. After addition of the base, the reaction mixture can be adjusted to within a temperature range of about 0°C to about room temperature and alcohols **6** can be added, preferably at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. Alcohols **6** can be diluted in an organic solvent or added in their undiluted form. The resulting reaction mixture is stirred until the reaction is substantially complete as determined by using an appropriate analytical method, preferably by gas chromatography, then the mono-protected diols **X** can be isolated by workup and purification.

Next, Scheme 1 outlines a method useful for synthesizing mono-protected diols X, wherein n is 1. First, compounds **7**, wherein E is a suitable leaving group, are reacted with compounds **8**, wherein R^1 and R^2 are as defined above and R^8 is H, $(C_1–C_6)$alkyl or (C_6)aryl, providing compounds **9**. Suitable leaving groups are well known in the art, for example, but not limited to halides, such as chloride, bromide, and iodide; aryl- or alkylsulfonyloxy, substituted arylsulfonyloxy (*e.g.*, tosyloxy or mesyloxy); substituted alkylsulfonyloxy (*e.g.*, haloalkylsulfonyloxy); (C_6)aryloxy or subsituted (C_6)aryloxy; and acyloxy groups. Compounds **7** are available commercially (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or can be prepared by well-known methods such as halogenation or sulfonation of butanediol. Compounds **8** are also available commercially (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or by well-known methods, such as those listed in Larock *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1999, pp. 1754-1755 and 1765. A review on alkylation of esters of type **8** is given by J. Mulzer in Comprehensive Organic Functional Transformations, Pergamon, Oxford 1995, pp. 148-151 and exemplary synthetic procedures for reacting compounds **7** with compounds **8** are described in United States Patent No. 5,648,387, column 6 and Ackerly, *et al.*, *J. Med. Chem.* **1995**, pp. 1608, all of which citations are hereby expressly incorporated herein by reference. The reaction requires the presence of a suitable base. Preferably, a suitable base will have a pK_a of greater than about 25, more preferably greater than about 30. Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*–butyllithium, *tert*–butyllithium, *sec*–butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; hydride bases such as sodium hydride and potassium hydride. Metal amide bases, such as lithium diisopropylamide are preferred. Preferably, to react compounds **7** with compounds **8**, a solution of about 1 to about 2 equivalents of a suitable base is added to a stirred solution comprising esters **8** and a suitable organic solvent, under an inert atmosphere, the solution maintained at a constant temperature within the range of about –95 °C to about room temperature, preferably at about –78 °C to about –20°C. Preferably, the base is diluted in a suitable organic solvent before addition. Preferably, the base is added at a rate of about 1.5 moles per hour. Organic solvents suitable for the reaction of compounds **7** with the compounds **8** include, but are not limited to, dichloromethane, diethyl ether, tetrahydrofuran, dimethylformamide, dimethyl sulfoxide, benzene, toluene, xylene, hydrocarbon solvents (*e.g.*, pentane, hexane, and heptane), and mixtures thereof. After

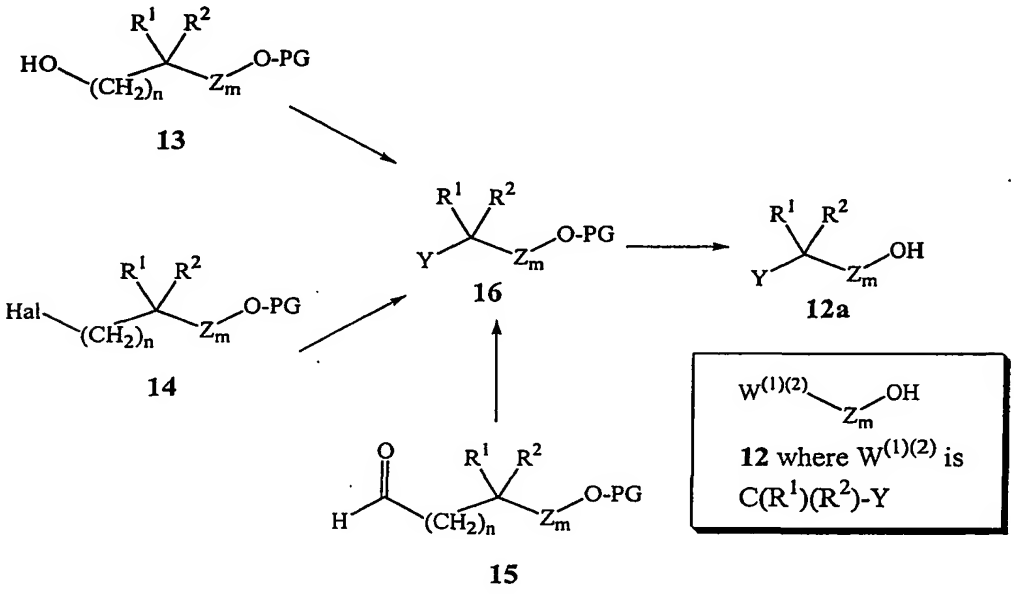
addition of the base, the reaction mixture is allowed to stir for about 1 to about 2 hours, and a compound **7**, preferably dissolved in a suitable organic solvent, is added, preferably at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. After addition of compounds **7**, the reaction-mixture temperature can be adjusted to within a temperature range of about –20 °C to about room temperature, preferably to about room temperature, and the reaction mixture is allowed to stir until the reaction is substantially complete as determined by using an appropriated analytical method, preferably thin-layer chromatography or high-performance liquid chromatography. Then the reaction mixture is quenched and compounds **9**, wherein n is 1 can be isolated by workup. Compounds **10** are then synthesized by reacting compounds **9** with $^{-}$O–PG according to the protocol described above for reacting alcohols **6** with $^{-}$O–PG. Next, compounds **10** can be converted to mono-protected diols **X**, wherein n is 1, by reduction of the ester group of compounds **10** to an alcohol group with a suitable reducing agent. A wide variety of reagents are available for reduction of such esters to alcohols, *e.g.*, see M. Hudlicky, *Reductions in Organic Chemistry*, 2nd ed., 1996 pp. 212-217, hereby expressly incorporated herein by reference. Preferably, the reduction is effected with a hydride type reducing agent, for example, lithium aluminum hydride, lithium borohydride, lithium triethyl borohydride, diisobutylaluminum hydride, lithium trimethoxyaluminum hydride, or sodium *bis*(2-methoxy)aluminum hydride. For exemplary procedures for reducing esters to alcohols, see Nystrom *et al.*, 1947, *J. Am. Chem. Soc.* 69:1197; and Moffet *et al.*, 1963, *Org. Synth., Collect.* 834(4), lithium aluminum hydride; Brown *et al.*,1965, *J. Am. Chem. Soc.* 87:5614, lithium trimethoxyaluminum hydride; Cerny *et al.*, 1969, *Collect. Czech. Chem. Commun.* 34:1025, sodium *bis*(2-methoxy)aluminum hydride; Nystrom *et al.*, 1949, *J. Am. Chem.* 71:245, lithium borohydride; and Brown *et al.*, 1980, *J. Org. Chem.* 45:1, lithium triethyl borohydride, all of which citations are hereby expressly incorporated herein by reference. Preferably, the reduction is conducted by adding an organic solution of compounds **10** to a stirred mixture comprising a reducing agent, preferably lithium aluminum hydride, and an organic solvent. During the addition, the reaction mixture is maintained at a constant temperature within the range of about -20 °C to about 80 °C, preferably at about room temperature. Organic solvents suitable for reacting **9** with –OPG include, but are not limited to, dichloromethane, diethyl ether, tetrahydrofuran or mixtures thereof, preferably tetrahydrofuran. After the addition, the reaction mixture is stirred at a constant temperature within the range of about room temperature to about 60°C, until the reaction is substantially complete as determined by using an appropriate analytical method, preferably thin-layer chromatography or high-performance-liquid chromatography.

Then the reaction mixture can be quenched and mono-protected diols **X**, wherein n is 1, can be isolated by workup and purification.

Scheme 1 next illustrates a three step synthetic sequence for homologating mono-protected diols **X** comprising: (a) halogenation (converting $-CH_2OH$ to $-CH_2-Hal$); (b) carbonylation (replacing –Hal with –CHO); and (c) reduction (converting –CHO to $-CH_2OH$), wherein a reaction sequence of (a), (b), and (c) increases the value of n by 1. In step (a) protected halo-alcohols **11**, wherein Hal is a halide selected from the group of chloro, bromo, or iodo, preferably iodo, can be prepared by halogenating mono-protected diols **X**, by using well-known methods (for a discussion of various methods for conversion of alcohols to halides see March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 431-433, hereby expressly incorporated herein by reference). For example, protected iodo-alcohols **11** can be synthesized starting from mono-protected diols **X** by treatment with Ph_3/I_2/imidazole (Garegg *et al.*, 1980, *J.C.S Perkin I* 2866); 1,2-dipheneylene phosphorochloridite/I_2 (Corey *et al.*, 1967, *J. Org. Chem.* 82:4160); or preferably with Me_3SiCl/NaI (Olah *et al.*, 1979, *J. Org. Chem.* 44:8, 1247), all of which citations are hereby expressly incorporated herein by reference. Step (b); carbonylation of alkyl halides, such as protected halo-alcohols **11**, is reviewed in Olah *et al.*, 1987, *Chem Rev.* 87:4, 671; and March, J., *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 483-484, both of which are hereby expressly incorporated herein by reference). Protected halo-alcohols **11** can be carbonylated with $Li(BF_3{\bullet}Et_2O)/HCONMe_2$ using the procedure described in Maddaford *et al.*, 1993, *J. Org. Chem.* 58:4132; Becker *et al.*, 1982, *J. Org. Chem.* 3297; or Myers *et al.*, 1992, *J. Am. Chem. Soc.* 114:9369 or, alternatively, with an organometallic/*N*-formylmorpholine using the procedure described in Olah *et al.*, 1984, *J. Org. Chem.* 49:3856 or Vogtle *et al.*, 1987, *J. Org. Chem.* 52:5560, all of which citations are hereby expressly incorporated herein by reference. The method described in Olah *et al.*, 1984, *J. Org. Chem.* 49:3856 is preferred. Reduction step (c) useful for synthesizing mono-protected diols **X** from aldehydes **12**, can be accomplished by well-known methods in the art for reduction of aldehydes to the corresponding alcohols (for a discussion see M. Hudlicky, *Reductions in Organic Chemistry*, 2nd ed., 1996 pp 137-139), for example, by catalytic hydrogenation (*see e.g.*, Carothers, 1949, *J. Am. Chem .Soc.* 46:1675) or, preferably by reacting aldehydes **12** with a hydride reducing agent, such as lithium aluminum hydride, lithium borohydride, sodium borohydride (*see e.g.*, the procedures described in Chaikin *et al.*, 1949, *J. Am. Chem. Soc.* 71:3245; Nystrom *et al.*, 1947, *J. Am. Chem. Soc.* 69:1197; and Nystrom *et al.*, 1949, *J. Am.*

Chem. 71:3245, all of which are hereby expressly incorporated herein by reference). Reduction with lithium aluminum hydride is preferred.

Scheme 2: Synthesis of Compounds of Formula 12a, which correspond to Compounds $W^{(1)(2)}$–Z_m–OH, Wherein $W^{(1)(2)}$ is $C(R^1)(R^2)$–Y



Scheme 2 outlines the method for the synthesis of protected alcohols **12a** wherein Y, R^1, R^2, Z, and m are defined as above. Protected alcohols **12a** correspond to compounds of the formula $W^{(1)(2)}$–Zm–OPG, wherein $W^{(1)(2)}$ is $C(R^1)(R^2)$–Y.

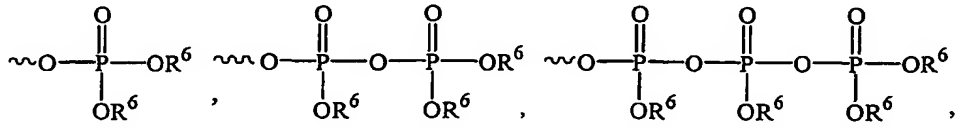
Protected alcohols **16**, wherein Y comprises a –COOH group, can be synthesized by oxidizing mono-protected diols X with an agent suitable for oxidizing a primary alcohol to a carboxylic acid (for a discussion see M. Hudlicky, *Oxidations in Organic Chemistry*, ACS Monograph 186, 1990, pp. 127-130, hereby expressly incorporated herein by reference). Suitable oxidizing agents include, but are not limited to, pyridinium dichromate (Corey *et al.*, 1979, *Tetrahedron Lett.* 399); manganese dioxide (Ahrens *et al.*, 1967, *J. Heterocycl. Chem.* 4:625); sodium permanganate monohydrate (Menger *et al.*, 1981, *Tetrahedron Lett.* 22:1655); and potassium permanganate (Sam *et al.*, 1972, *J. Am. Chem. Soc.* 94:4024), all of which citations are hereby expressly incorporated herein by reference. The preferred oxidizing reagent is pyridinium dichromate. In an alternative synthetic procedure, protected alcohols **16**, wherein Y comprises a –COOH group, can be synthesized by treatment of protected halo-alcohols **14**, wherein X is iodo, with CO or CO_2, as described in Bailey *et al.*, 1990, *J. Org. Chem.* 55:5404 and Yanagisawa *et al.*, 1994, *J. Am. Chem. Soc.* 116:6130,

the two of which citations are hereby expressly incorporated herein by reference. Protected alcohols **16**, wherein Y comprises –C(O)OR^5, wherein R^5 is as defined above, can be synthesized by oxidation of mono-protected diols **X** in the presence of R^5OH (see generally, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 1196). An exemplary procedure for such an oxidation is described in Stevens *et al.*, 1982, *Tetrahedron Lett.* 23:4647 (HOCl); Sundararaman *et al.*, 1978, *Tetrahedron Lett.* 1627 (O_3/KOH); Wilson *et al.*, 1982, *J. Org. Chem.* 47:1360 (*t*–BuOOH/Et_3N); and Williams *et al.*, 1988, *Tetrahedron Lett.* 29:5087 (Br_2), the four of which citations are hereby expressly incorporated herein by reference. Preferably, protected alcohols **16**, wherein Y comprises a –C(O)OR^5 group are synthesized from the corresponding carboxylic acid (*i.e.*, **16**, wherein Y comprises –COOH) by esterification with R^5OH (*e.g., see* March, J., *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 393-394, hereby expressly incorporated herein by reference). In another alternative synthesis, protected alcohols **16**, wherein Y comprises –C(O)OR^5, can be prepared from protected halo-alcohols **14** by carbonylation with transition metal complexes (*see e.g.*, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 484-486; Urata *et al.*, 1991, *Tetrahedron Lett.* 32:36, 4733); and Ogata *et al.*, 1969, *J. Org. Chem.* 3985, the three of which citations are hereby expressly incorporated herein by reference).

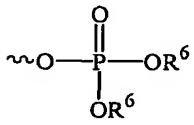
Protected alcohols **16**, wherein Y comprises –O$C(O)R^5$, wherein R^5 is as defined above, can be prepared by acylation of mono-protected diols **X** with a carboxylate equivalent such as an acyl halide (*i.e.*, $R^5C(O)$–Hal, wherein Hal is iodo, bromo, or chloro, *see e.g.*, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 392 and *Org. Synth. Coll.* Vol. III, Wiley, NY, pp. 142, 144, 167, and 187 (1955)) or an anhydride (*i.e.*, $R^5C(O)$–O–(O)CR^5, see *e.g.*, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 392-393 and *Org. Synth. Coll.* Vol. III, Wiley, NY, pp. 11, 127, 141, 169, 237, 281, 428, 432, 690, and 833 (1955), all of which citations are hereby expressly incorporated herein by reference). Preferably, the reaction is conducted by adding a base to a solution comprising mono-protected diols **X**, a carboxylate equivalent, and an organic solvent, which solution is preferably maintained at a constant temperature within the range of 0°C to about room temperature. Solvents suitable for reacting mono-protected diols **X** with a carboxylate equivalent include, but are not limited to, dichloromethane, toluene, and ether, preferably dichloromethane. Suitable bases include, but are not limited to, hydroxide sources, such as sodium hydroxide, potassium hydroxide, sodium carbonate, or potassium carbonate; or an amine such as triethylamine, pyridine, or dimethylaminopyridine, amines are preferred. The progress of the reaction can

be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance liquid chromatography and when substantially complete, the product can be isolated by workup and purified if desired.

Protected alcohols **16**, wherein Y comprises one of the following phosphate ester groups



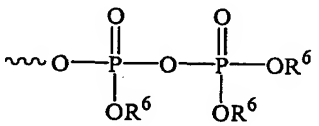
wherein R^6 is defined as above, can be prepared by phosphorylation of mono-protected diols **X** according to well-known methods (for a general reviews, see Corbridge *Phosphorus: An Outline of its Chemistry, Biochemistry, and Uses*, Studies in Inorganic Chemistry, 3rd ed., pp. 357-395 (1985); Ramirez *et al.*, 1978, *Acc. Chem. Res.* 11:239; and Kalckare *Biological Phosphorylations*, Prentice-Hall, New York (1969); J. B. Sweeny in *Comprehensive Organic Functional Group Transformations*, A.R. Katritzky, O. Meth-Cohn and C.W. Rees, Eds. Pergamon: Oxford, 1995, vol 2, pp. 104-109, the four of which are hereby expressly incorporated herein by reference). Protected alcohols **16** wherein Y comprises a monophosphate group of the formula:



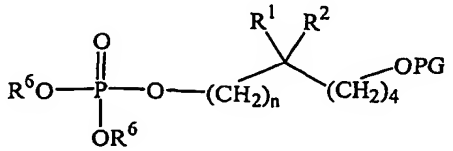
wherein R^6 is defined as above, can be prepared by treatment of mono-protected diol **X** with phosphorous oxychloride in a suitable solvent, such as xylene or toluene, at a constant temperature within the range of about 100°C to about 150°C for about 2 hours to about 24 hours. After the reaction is deemed substantially complete, by using an appropriate analytical method, the reaction mixture is hydrolyzed with R^6–OH. Suitable procedures are referenced in Houben-Weyl, Methoden der Organische Chemie, Georg Thieme Verlag Stuttgart 1964, vol. XII/2, pp. 143-210 and 872-879, hereby expressly incorporated herein by reference. Alternatively, when both R^6 are hydrogen, can be synthesized by reacting mono-protected diols **X** with silyl polyphosphate (Okamoto *et al.*, 1985, *Bull Chem. Soc. Jpn.* 58:3393, hereby expressly incorporated herein by reference) or by hydrogenolysis of their benzyl or phenyl esters (Chen *et al.*, 1998, *J. Org. Chem.* 63:6511, hereby expressly

incorporated herein by reference). In another alternative procedure, when R^6 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl, the monophosphate esters can be prepared by reacting mono-protected diols **X** with appropriately substituted phophoramidites followed by oxidation of the intermediate with *m*-chloroperbenzoic acid (Yu *et al.*, 1988, *Tetrahedron Lett.* 29:979, hereby expressly incorporated herein by reference) or by reacting mono-protected diols **X** with dialkyl or diaryl substituted phosphorochloridates (Pop, *et al*, 1997, *Org. Prep. and Proc. Int.* 29:341, hereby expressly incorporated herein by reference). The phosphoramidites are commercially available (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or readily prepared according to literature procedures (*see e.g.*, Uhlmann *et al.* 1986, *Tetrahedron Lett.* 27:1023 and Tanaka *et al.*, 1988, *Tetrahedron Lett.* 29:199, both of which are hereby expressly incorporated herein by reference). The phosphorochloridates are also commercially available (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or prepared according to literature methods (*e.g.*, Gajda *et al*, 1995, *Synthesis* 25:4099. In still another alternative synthesis, protected alcohols **16**, wherein Y comprises a monophosphate group and R^6 is alkyl or aryl, can be prepared by reacting $IP^+(OR^6)_3$ with mono-protected diols **X** according to the procedure described in Stowell *et al.*, 1995, *Tetrahedron Lett.* 36:11, 1825 or by alkylation of protected halo alcohols **14** with the appropriate dialkyl or diaryl phosphates (*see e.g.*, Okamoto, 1985, *Bull Chem. Soc. Jpn.* 58:3393, hereby expressly incorporated herein by reference).

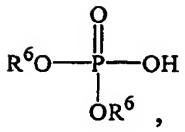
Protected alcohols **16** wherein Y comprises a diphosphate group of the formula



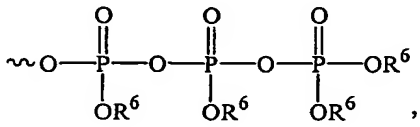
wherein R^6 is defined as above, can be synthesized by reacting the above-discussed monophosphates of the formula:



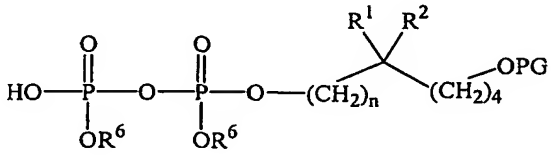
with a phosphate of the formula



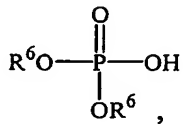
(commercially available, *e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin), in the presence of carbodiimide such as dicyclohexylcarbodiimide, as described in Houben-Weyl, *Methoden der Organische Chemie*, Georg Thieme Verlag Stuttgart 1964, vol. XII/2, pp. 881-885. In the same fashion, protected alcohols **16**, wherein Y comprises a triphosphate group of the formula:



can be synthesized by reacting the above-discussed diphosphate protected alcohols, of the formula:

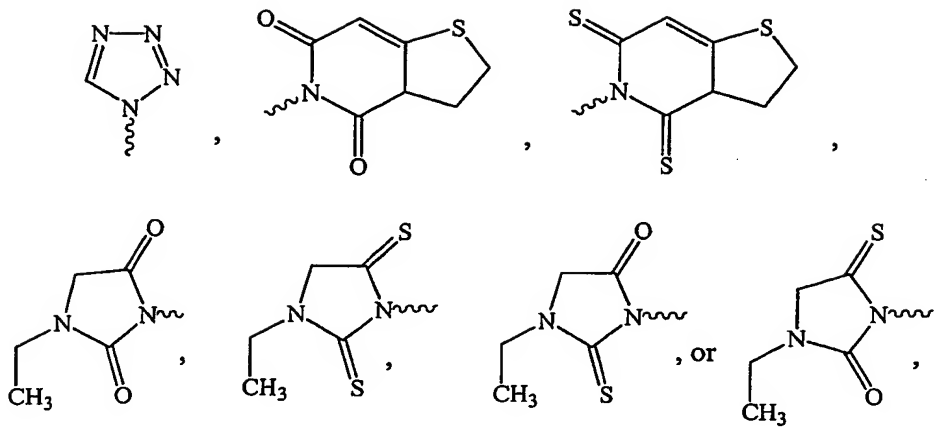


with a phosphate of the formula:



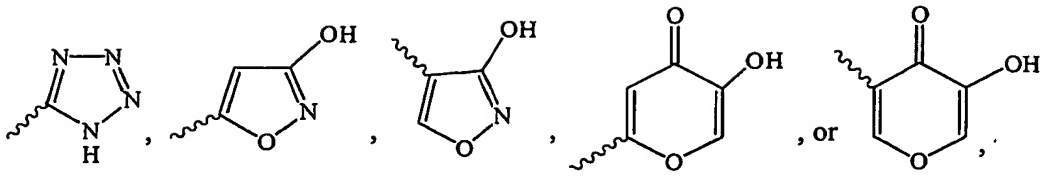
as described above. Alternatively, when R^6 is H, protected alcohols **16** wherein Y comprises the triphosphate group, can be prepared by reacting mono-protected diols **X** with salicyl phosphorochloridite and then pyrophosphate and subsequent cleavage of the adduct thus obtained with iodine in pyridine as described in Ludwig *et al.*, 1989, *J. Org. Chem.* 54:631, hereby expressly incorporated herein by reference.

Protected alcohols **16**, wherein Y is $-SO_3H$ or a heterocyclic group selected from the group consisting of:



can be prepared by halide displacement from protected halo-alcohols **14**. Thus, when Y is $-SO_3H$, protected alcohols **16** can by synthesized by reacting protected halo-alcohols **14** with sodium sulfite as described in Gilbert *Sulfonation and Related Reactions*; Wiley: New York, 1965, pp. 136-148 and pp. 161-163; *Org. Synth. Coll.* Vol. II, Wiley, NY, 558, 564 (1943); and *Org. Synth. Coll.* Vol. IV, Wiley, NY, 529 (1963), all three of which are hereby expressly incorporated herein by reference. When Y is one of the above-mentioned heterocycles, protected alcohols **16** can be prepared by reacting protected halo-alcohols **14** with the corresponding heterocycle in the presence of a base. The heterocycles are available commercially (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or prepared by well-known synthetic methods (see the procedures described in Ware, 1950, *Chem. Rev.* 46:403-470, hereby expressly incorporated herein by reference). Preferably, the reaction is conducted by stirring a mixture comprising **14**, the heterocycle, and a solvent at a constant temperature within the range of about room temperature to about 100°C, preferably within the range of about 50°C to about 70°C for about 10 to about 48 hours. Suitable bases include hydroxide bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, or potassium carbonate. Preferably, the solvent used in forming protected alcohols **16** is selected from dimethylformamide; formamide; dimethyl sulfoxide; alcohols, such as methanol or ethanol; and mixtures thereof. The progress of the reaction can be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance liquid chromatography and when substantially complete, the product can be isolated by workup and purified if desired.

Protected alcohols **16**, wherein Y is a heteroaryl ring selected from

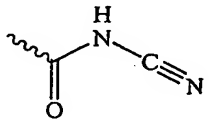


can be prepared by metallating the suitable heteroaryl ring then reacting the resulting metallated heteroaryl ring with protected halo-alcohols **14** (for a review, see Katritzky *Handbook of Heterocyclic Chemistry*, Pergamon Press: Oxford 1985). The heteroaryl rings are available commercially or prepared by well-known synthetic methods (*see e.g.*, Joule *et al., Heterocyclic Chemistry*, 3rd ed., 1995; De Sarlo *et al.*, 1971, *J. Chem. Soc. (C)* 86; Oster *et al.*, 1983, *J. Org. Chem.* 48:4307; Iwai *et al.*, 1966, *Chem. Pharm. Bull.* 14:1277; and United States Patent No. 3,152,148, all of which citations are hereby expressly incorporated herein by reference). As used herein, the term "metallating" means the forming of a carbon-metal bond, which bond may be substantially ionic in character. Metallation can be accomplished by adding about 2 equivalents of strong organometallic base, preferably with a pK_a of about 25 or more, more preferably with a pK_a of greater than about 35, to a mixture comprising a suitable organic solvent and the heterocycle. Two equivalents of base are required: one equivalent of the base deprotonates the –OH group or the –NH group, and the second equivalent metallates the heteroaryl ring. Alternatively, the hydroxy group of the heteroaryl ring can be protected with a base-stable, acid-labile protecting group as described in Greene, T.W., *Protective Groups in Organic Synthesis*, 3rd edition 17-237 (1999), hereby expressly incorporated herein by reference. Where the hydroxy group is protected, only one equivalent of base is required. Examples of suitable base-stable, acid-labile hydroxyl-protecting groups, include but are not limited to, ethers, such as methyl, methoxy methyl, methylthiomethyl, methoxyethoxymethyl, *bis*(2-chloroethoxy)methyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahyrofuranyl, tetrahydrothiofuranyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, *t*-butyl, allyl, benzyl, *o*-nitrobenzyl, triphenylmethyl, α-naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, 9-(9-phenyl-10-oxo)anthranyl, trimethylsilyl, isopropyldimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl; and esters, such as pivaloate, adamantoate, and 2,4,6-trimethylbenzoate. Ethers are preferred, particularly straight chain ethers, such as methyl ether, methoxymethyl ether, methylthiomethyl ether, methoxyethoxymethyl ether, *bis*(2-chloroethoxy)methyl ether. Preferably, the pK_a of the base is higher than the pK_a of the

proton of the heterocycle to be deprotonated. For a listing of pK_as for various heteroaryl rings, see Fraser *et al.*, 1985, *Can. J. Chem.* 63:3505, hereby expressly incorporated herein by reference. Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*–butyllithium, *tert*–butyllithium, *sec*–butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium hydride and potassium hydride. If desired, the organometallic base can be activated with a complexing agent, such as *N,N,N',N'*–tetramethylethylenediamine or hexamethylphosphoramide (1970, *J. Am. Chem. Soc.* 92:4664, hereby expressly incorporated herein by reference). Solvents suitable for synthesizing protected alcohols **16**, wherein Y is a heteroaryl ring include, but are not limited to, diethyl ether; tetrahydrofuran; and hydrocarbons, such as pentane. Generally, metallation occurs alpha to the heteroatom due to the inductive effect of the heteroatom, however, modification of conditions, such as the identity of the base and solvents, order of reagent addition, reagent addition times, and reaction and addition temperatures can be modified by one of skill in the art to achieve the desired metallation position (*see e.g.*, Joule *et al., Heterocyclic Chemistry*, 3rd ed., 1995, pp. 30-42, hereby expressly incorporated herein by reference) Alternatively, the position of metallation can be controlled by use of a halogenated heteroaryl group, wherein the halogen is located on the position of the heteroaryl ring where metallation is desired (*see e.g.*, Joule *et al., Heterocyclic Chemistry*, 3rd ed., 1995, p. 33 and Saulnier *et al.*, 1982, *J. Org. Chem.* 47:757, the two of which citations are hereby expressly incorporated herein by reference). Halogenated heteroaryl groups are available commercially (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or can be prepared by well-known synthetic methods (*see e.g.*, Joule *et al., Heterocyclic Chemistry*, 3rd ed., 1995, pp. 78, 85, 122, 193, 234, 261, 280, 308, hereby expressly incorporated herein by reference). After metallation, the reaction mixture comprising the metallated heteroaryl ring is adjusted to within a temperature range of about 0°C to about room temperature and protected halo-alcohols **14** (diluted with a solvent or in undiluted form) are added, preferably at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. After addition of protected halo-alcohols **14**, the reaction mixture is stirred at a constant temperature within the range of about room temperature and about the solvent's boiling temperature and the reaction's progress can be monitored by the appropriate analytical technique, preferably thin-layer chromatography or high-performance liquid chromatography. After the reaction

is substantially complete, protected alcohols **16** can be isolated by workup and purification. It is to be understood that conditions, such as the identity of protected halo-alcohol **14**, the base, solvents, orders of reagent addition, times, and temperatures, can be modified by one of skill in the art to optimize the yield and selectivity. Exemplary procedures that can be used in such a transformation are described in Shirley *et al.*, 1995, *J. Org. Chem.* 20:225; Chadwick *et al.*, 1979, *J. Chem. Soc., Perkin Trans. 1* 2845; Rewcastle, 1993, *Adv. Het. Chem.* 56:208; Katritzky *et al.*, 1993, *Adv. Het. Chem.* 56:155; and Kessar *et al.*, 1997, *Chem. Rev.* 97:721.

When Y is



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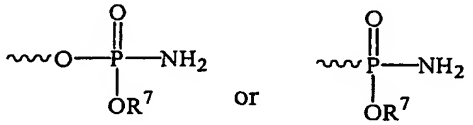
protected alcohols **16** can be prepared from their corresponding carboxylic acid derivatives (**16**, wherein Y is $-CO_2H$) as described in Belletire *et al*, 1988, *Synthetic Commun.* 18:2063 or from the corresponding acylchlorides (**16**, wherein Y is –CO–halo) as described in Skinner *et al.*, 1995, *J. Am. Chem. Soc.* 77:5440, both citations are hereby expressly incorporated herein by reference. The acylhalides can be prepared from the carboxylic acids by well known procedures such as those described in March, J., *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 437-438, hereby expressly incorporated herein by reference. When Y is



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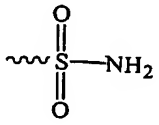
wherein R^7 is as defined above, protected alcohols **16** can be prepared by first reacting protected halo-alcohols **15** with a trialkyl phosphite according to the procedure described in Kosolapoff, 1951, *Org. React.* 6:273 followed by reacting the derived phosphonic diester with ammonia according to the procedure described in Smith *et al.*, 1957, *J. Org. Chem.* 22:265, hereby expressly incorporated herein by reference. When Y is



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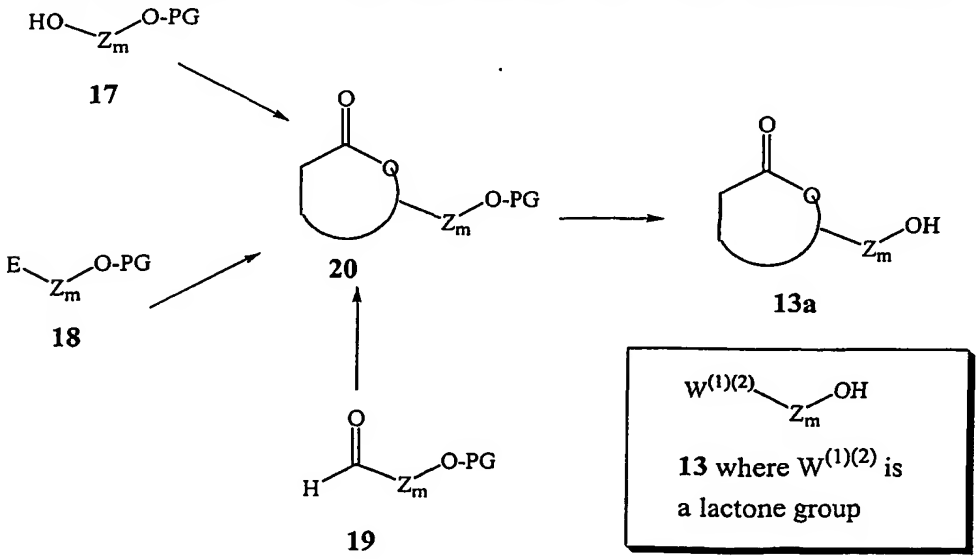
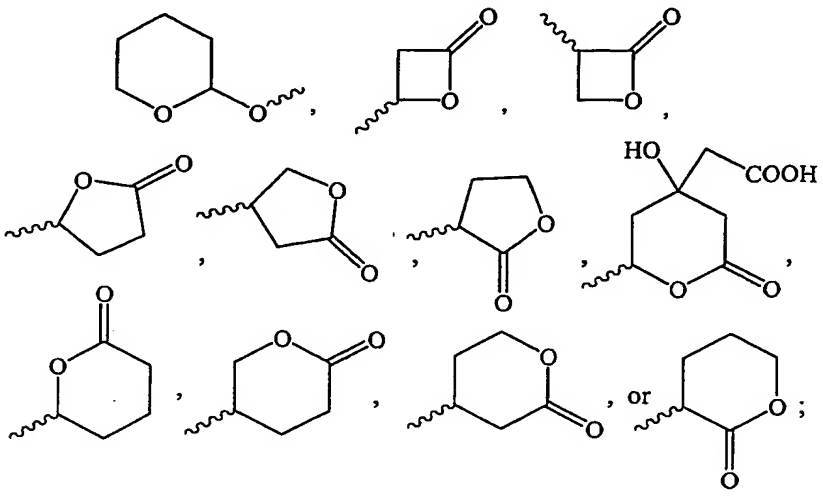
protected alcohols **16** can be prepared by reacting their sulphonic acid derivatives (*i.e.*, **16**, wherein Y is $-SO_3H$) with ammonia as described in Sianesi *et al.*, 1971, *Chem. Ber.* 104:1880 and Campagna *et al.*, 1994, *Farmaco, Ed. Sci.* 49:653, both of which citations are hereby expressly incorporated herein by reference).

As further illustrated in Scheme 2, protected alcohols **16** can be deprotected providing alcohols **20a**. The deprotection method depends on the identity of the alcohol-protecting group, *see e.g.*, the procedures listed in Greene, T.W., *Protective Groups in Organic Synthesis*, 3rd edition 17-237 (1999), particularly see pages 48-49, hereby expressly incorporated herein by reference. One of skill in the art will readily be able to choose the appropriate deprotection procedure. When the alcohol is protected as an ether function (*e.g.*, methoxymethyl ether), the alcohol is preferably deprotected with aqueous or alcoholic acid. Suitable deprotection reagents include, but are not limited to, aqueous hydrochloric acid, *p*-toluenesulfonic acid in methanol, pyridinium-*p*-toluenesulfonate in ethanol, Amberlyst H–15 in methanol, boric acid in ethylene-glycol-monoethylether, acetic acid in a water–tetrahydrofuran mixture, aqueous hydrochloric acid is preferred. Examples of such procedures are described, respectively, in Bernady *et al.*, 1979, *J. Org. Chem.* 44:1438; Miyashita *et al.*, 1977, *J. Org. Chem.* 42:3772; Johnston *et al.*, 1988, *Synthesis* 393; Bongini *et al.*, 1979, *Synthesis* 618; and Hoyer *et al.*, 1986, *Synthesis* 655; Gigg *et al.*, 1967, *J. Chem. Soc. C*, 431; and Corey *et al.*, 1978, *J. Am. Chem. Soc.* 100:1942, all of which are hereby expressly incorporated herein by reference.

Scheme 3: Synthesis of Compounds of Formula 13a, which correspond to $W^{(1)(2)}$–Z_m–OH, Wherein $W^{(1)(2)}$ is a Lactone Group

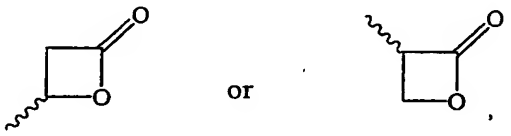


Scheme 3 depicts the synthesis of protected lactone alcohols **20** and lactone alcohols **13a**. Compounds **20** and **13a** correspond to compounds of the formula $W^{(1)(2)}$–Zm–OPG and $W^{(1)(2)}$–Z_m–OH respectively, wherein $W^{(1)(2)}$ is a lactone group selected from:



Protected lactone alcohols **20** can be prepared from compounds of the formula **17**, **18**, or **19** by using well-known condensation reactions and variations of the Michael reaction. Methods for the synthesis of lactones are disclosed in Multzer in *Comprehensive Organic Functional Group Transformations*, A.R. Katritzky, O. Meth-Cohn and C.W. Rees, Eds. Pergamon: Oxford, 1995, vol 5, pp. 161-173, hereby expressly incorporated herein by reference. Mono-protected diols **19**, electrophilic protected alcohols **18**, and aldehydes **19** are readily available ether commercially (*e.g.*, Aldrich Chemical Co., Milwaukee, WI) or by well known synthetic procedures.

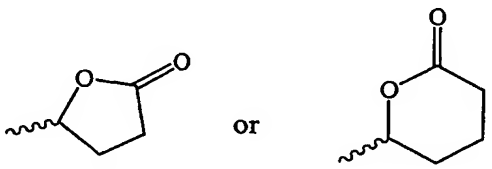
When $W^{(1)(2)}$ is a beta-lactone group of the formula:



3-beta-lactone 4-beta-lactone

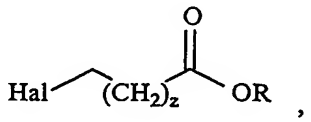
protected lactone alcohols **20** can be prepared from aldehydes **19** and electrophilic protected alcohols **18**, respectively, by a one-pot-addition-lactonization according to the procedure of Masamune *et al.*, 1976, *J. Am. Chem. Soc.* 98:7874 and Danheiser *et al.*, 1991, *J. Org. Chem.* 56:1176, both of which are hereby expressly incorporated herein by reference. This one-pot-addition-lactonization methodology has been reviewed by Multzer in *Comprehensive*

Organic Functional Group Transformations, A.R. Katritzky, O. Meth-Cohn and C.W. Rees, Eds. Pergamon: Oxford, 1995, vol 5, pp. 161, hereby expressly incorporated herein by reference When $W^{(1)(2)}$ is a gamma- or delta-lactone group of the formula:



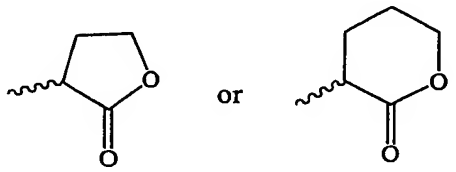
gamma-lactone or delta-lactone

protected lactone alcohols **20** can be prepared from aldehydes **19** according to well known synthetic methodology. For example, the methodology described in Masuyama *et al.*, 2000, *J. Org. Chem.* 65:494; Eisch *et al.*,1978, *J. Organo. Met. Chem. C8* 160; Eaton *et al.*, 1947, *J. Org. Chem.* 37:1947;Yunker *et al.*, 1978, *Tetrahedron Lett.* 4651; Bhanot *et al.*,1977, *J. Org. Chem.* 42:1623; Ehlinger *et al.*, 1980, *J. Am. Chem. Soc.* 102:5004; and Raunio *et al.*, 1957, *J. Org. Chem.* 22:570, all of which citations are hereby expressly incorporated herein by reference. For instance, as described in Masuyama *et al.*,2000, *J. Org. Chem.* 65:494, aldehydes **19** can be treated with about 1 equivalent of a strong organometallic base, preferably with a pK_a of about 25 or more, more preferably with a pK_a of greater than about 35, in a suitable organic solvent to give a reaction mixture. Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*–butyllithium, *tert*–butyllithium, *sec*–butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium hydride and potassium hydride, preferably lithium tetramethylpiperidide. Suitable solvents include, but are not limited to, diethyl ether and tetrahydrofuran. The reaction-mixture temperature is adjusted to within the range of about 0°C to about 100°C, preferably about room temperature to about 50°C, and a halide of the formula:



wherein z is 1 or 2 (diluted with a solvent or in undiluted form) is added. The reaction mixture is stirred for a period of about 2 hours to about 48 hours, preferably about 5 to about 10 hours, during which time the reaction's progress can be followed by using an appropriate

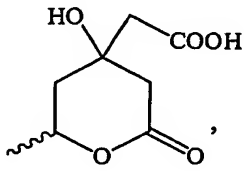
analytical technique, such as thin layer chromatography or high performance liquid chromatography. When the reaction is deemed substantially complete, protected lactone alcohols **20** can be isolated by workup and purified if desired. When $W^{(1)(2)}$ is a gamma- or delta-lactone group of the formula:



gamma-lactone or delta-lactone

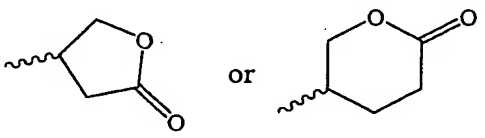
protected lactone alcohols **20** can be synthesized by deprotonating the corresponding lactone with a strong base providing the lactone enolate and reacting the enolate with electrophilic protected alcohols **20** (for a detailed discussion of enolate formation of active methylene compounds such as lactones, see House *Modern Synthetic Reactions*; W. A. Benjamin, Inc. Philippines 1972 pp. 492-570, and for a discussion of reaction of lactone enolates with electrophiles such as carbonyl compounds, see March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 944-945, both of which are hereby expressly incorporated herein by reference). Lactone-enolate formation can be accomplished by adding about 1 equivalent of a strong organometallic base, preferably with a pK_a of about 25 or more, more preferably with a pK_a of greater than about 35, to a mixture comprising a suitable organic solvent and the lactone. Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*–butyllithium, *tert*–butyllithium, *sec*–butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium hydride and potassium hydride, preferably lithium tetramethylpiperidide. Solvents suitable for lactone-enolate formation include, but are not limited to, diethyl ether and tetrahydrofuran. After enolate formation, the reaction-mixture temperature is adjusted to within the range of about –78°C to about room temperature, preferably about –50°C to about 0°C, and electrophilic protected alcohols **18** (diluted with a solvent or in undiluted form) are added, preferably at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. The reaction mixture is stirred for a period of about 15 minutes to about 5 hours, during which time the reaction's progress can be followed by using an appropriate analytical technique, such as thin layer

chromatography or high performance liquid chromatography. When the reaction is deemed substantially complete, protected lactone alcohols **20** can be isolated by workup and purified if desired. When $W^{(1)(2)}$ is a lactone group of the formula:



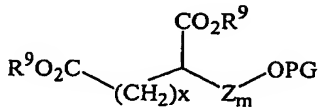
protected lactone alcohols **20** can be prepared from aldehydes **19** according to the procedure described in United States Patent No. 4,622,338, hereby expressly incorporated herein by reference.

When $W^{(1)(2)}$ is a gamma- or delta-lactone group of the formula:



gamma-lactone delta-lactone

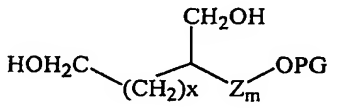
protected lactone alcohols **20** can be prepared according to a three step sequence. The first step comprises base-mediated reaction of electrophilic protected alcohols **18** with succinic acid esters (*i.e.*, $R^9O_2CCH_2CH_2CO_2R^9$, wherein R^9 is alkyl) or glutaric acid esters (*i.e.*, $R^9O_2CCH_2CH_2CH_2CO_2R^9$, wherein R^9 is alkyl) providing a diester intermediate of the formula **21**:



21

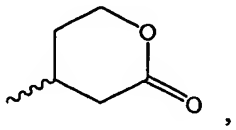
wherein x is 1 or 2 depending on whether the gamma or delta lactone group is desired. The reaction can be performed by adding about 1 equivalent of a strong organometallic base, preferably with a pK_a of about 25 or more, more preferably with a pK_a of greater than about 35, to a mixture comprising a suitable organic solvent and the succinic or glutaric acid ester. Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*–butyllithium, *tert*–butyllithium, *sec*–butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium

amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium hydride and potassium hydride, preferably lithium tetramethylpiperidide. Suitable solvents include, but are not limited to, diethyl ether and tetrahydrofuran. After enolate formation, the reaction-mixture temperature is adjusted to within the range of about –78°C to about room temperature, preferably about –50°C to about 0°C, and electrophilic protected alcohols **18** (diluted with a solvent or in undiluted form) are added, preferably at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. The reaction mixture is stirred for a period of about 15 minutes to about 5 hours, during which time the reaction's progress can be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance liquid chromatography. When the reaction is deemed substantially complete, the diester intermediate be isolated by workup and purified if desired. In the second step, the intermediate diester can be reduced, with a hydride reducing agent, to yield a diol of the formula **22**:



22

The reduction can be performed according to the procedures referenced in March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 1214, hereby expressly incorporated herein by reference). Suitable reducing agents include, but are not limited to, lithium aluminum hydride, diisobutylaluminum hydride, sodium borohydride, and lithium borohydride). In the third step, the diol can be oxidatively cyclized with $RuH_2(PPh_3)_4$ to the product protected lactone alcohols **20** according to the procedure of Yoshikawa *et al.*, 1986, *J. Org. Chem.* 51:2034 and Yoshikawa *et al.*, 1983, *Tetrahedron Lett.* 26:2677, both of which citations are hereby expressly incorporated herein by reference. When $W^{(1)(2)}$ is a lactone group of the formula:



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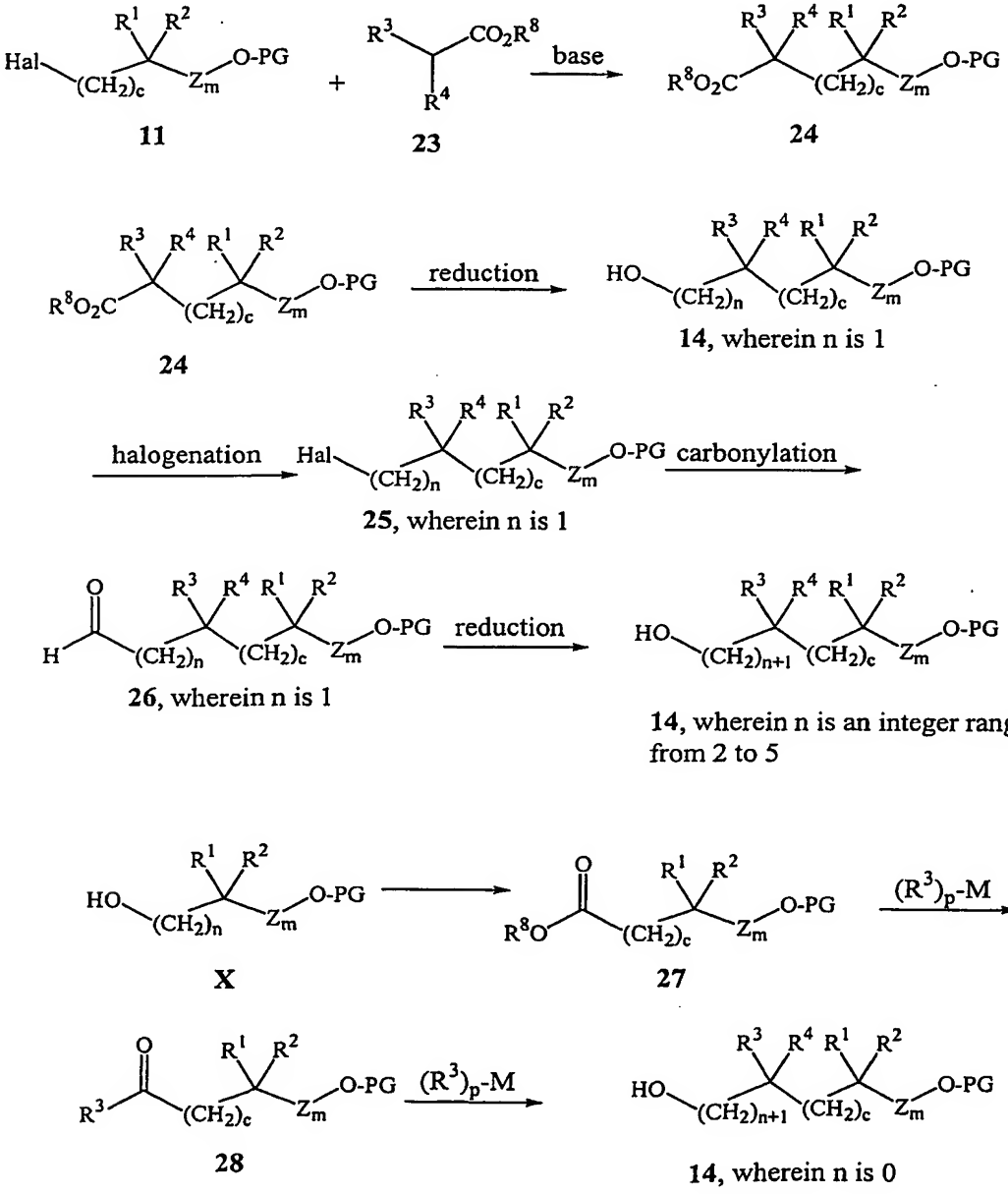
protected lactone alcohols **20** can be synthesized by reacting the Grignard salts of electrophilic protected alcohols **18**, where E is a halide, with 5,6-dihydro-2*H*-pyran-2-one, commercially available (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin), in the presence of catalytic amounts of a 1-dimethylaminoacetyl)pyrolidine-2yl)methyl-diarylphosphine-copper (I) iodide complex as described in Tomioka *et al.*, 1995, *Tetrahedron Lett.* 36:4275, hereby expressly incorporated herein by reference.

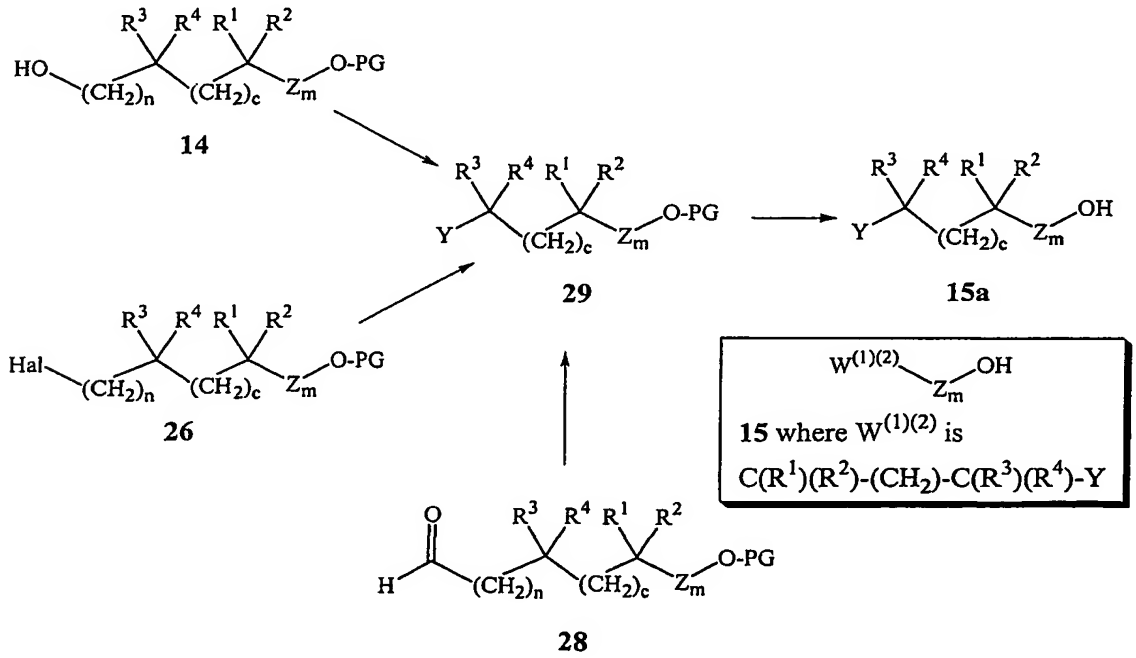
Scheme 4: Synthesis of Compounds of Formula 14



Scheme 4 outlines methodology for the synthesis of protected alcohols **14**. Compounds **14**, wherein n is an integer ranging from 1 to 5, can be prepared from compounds **11** using general synthetic strategy depicted and adapting the synthetic protocols from those discussed for Scheme 1.

Next, Scheme 4 depicts the general strategy for the synthesis of compounds **14** wherein n is 0. First, Esters **27**, wherein R^8 is as defined above, are synthesized by oxidation of mono-protected diols **X** in the presence of R^8OH (see generally, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 1196). An exemplary procedure for such an oxidation is described in Stevens *et al.*, 1982, *Tetrahedron Lett.* 23:4647 (HOCl); Sundararaman *et al.*, 1978, *Tetrahedron Lett.* 1627 (O_3/KOH); Wilson *et al.*, 1982, *J. Org. Chem.* 47:1360 (*t*–BuOOH/Et_3N); and Williams *et al.*, 1988, *Tetrahedron Lett.* 29:5087 (Br_2), the four of which citations are hereby expressly incorporated herein by reference. Compounds **28** are converted to compounds **14** wherein n is 0 by adapting the synthetic procedures depicted in Scheme 1.

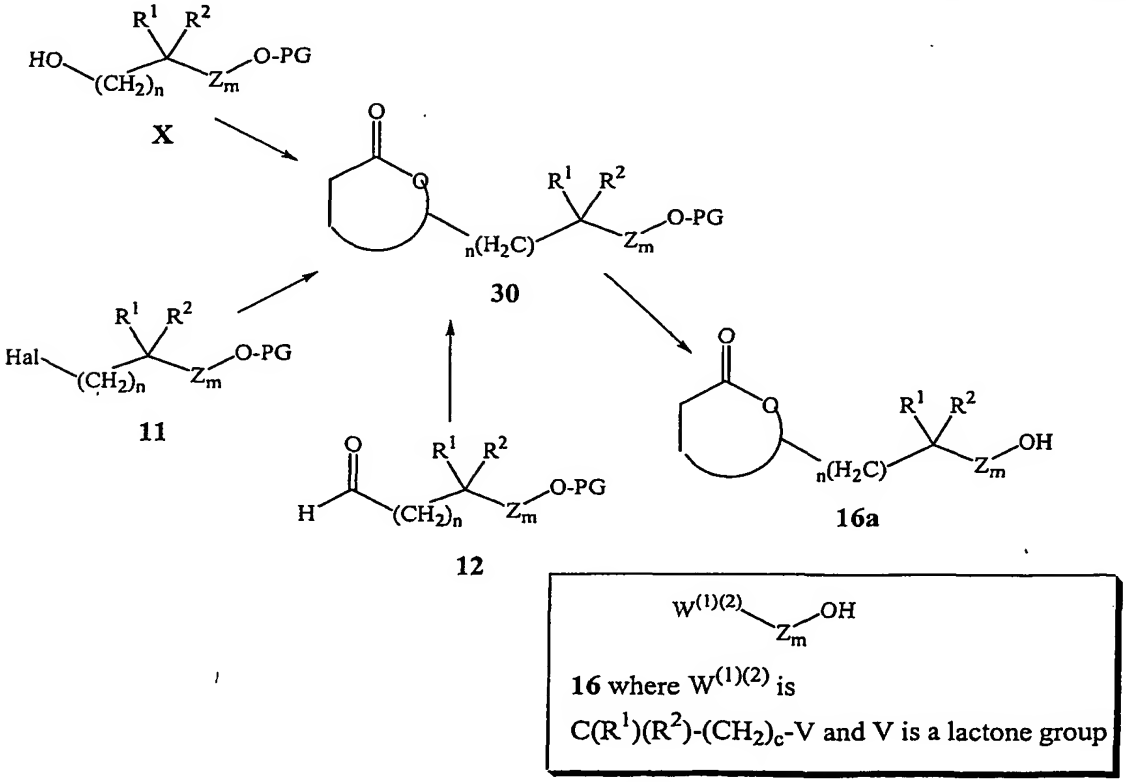
Scheme 5: Synthesis of Compounds of Formula 15a, which correspond to compounds $W^{(1)(2)}$–Z_m–OH, Where $W^{(1)(2)}$ is $C(R^1)(R^2)$–$(CH_2)_cC(R^3)(R^4)$–Y



Scheme 5 outlines methodology for the synthesis of protected alcohols **29** and alcohols **15a**, which correspond to $W^{(1)(2)}$–Z_m–OPG and $W^{(1)(2)}$–Z_m–OH, respectively, wherein $W^{(1)(2)}$ is $C(R^1)(R^2)$–$(CH_2)_cC(R^3)(R^4)$–Y. The synthesis of starting materials **14**, **26**,

and **28** are depicted in Scheme 4 and the synthetic methods and procedures can be adapted from those described for Scheme 2.

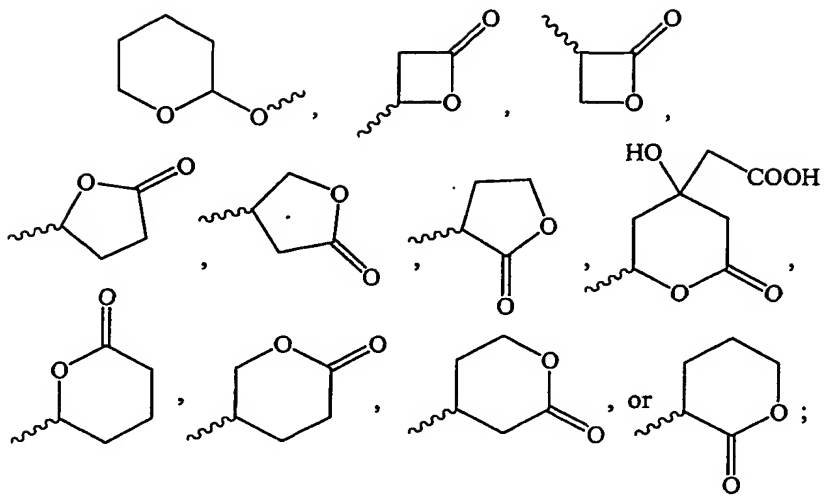
Scheme 6: Synthesis of Compounds of Formula 16, which correspond to compounds $W^{(1)(2)}$–Z_m–OH, Wherein $W^{(1)(2)}$ is $C(R^1)(R^2)(CH_2)_c$–V where V is a Lactone Group



$W^{(1)(2)}$–Z_m–OH

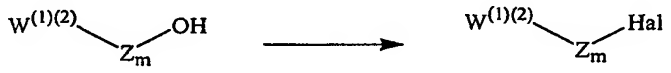
16 where $W^{(1)(2)}$ is $C(R^1)(R^2)$-$(CH_2)_c$-V and V is a lactone group

Scheme 6 depicts the synthesis of protected lactone alcohols **30** and lactone alcohols **16a**. Compounds **30** and **16a** correspond to compounds of the formula, which correspond to compounds $W^{(1)(2)}$–Z_m–OH, Wherein $W^{(1)(2)}$ is $C(R^1)(R^2)(CH2)_c$–V and V is a Group selected from:



As shown in Scheme 6, protected lactone alcohols **30** and lactone alcohols **16a** can be synthesized from compounds of the formula **X**, **11**, or **12** by adaptation of the methods and procedures discussed above for Scheme 3.

Scheme 7: Conversion of Alcohols 18 to Halides 18e



18 **18e**

Scheme 7 depicts the synthesis of halides **17**. Halides **17** can be synthesized by a variety of methods. One method involves conversion of the alcohol to a leaving group such as a sulfonic ester, such as, for example, tosylate, brosylate, mesylate, or nosylate. This intermediate is then treated with a source of X^-, wherein X^- is I^-, Br^-, or Cl^- in a solvent such as THF or ether. A general method for converting vinyl and phenyl alcohols to thiols involves initially converting the alcohol to a leaving group (*e.g.*, a tosylate) then treating with a halide nucleophile.

Scheme 8: Synthesis of Compounds of Formula I

17 31 I

Scheme 8 outlines the synthesis of compounds **I**. In the first step, compounds **I** are synthesized by reacting compounds **17** (compounds **X 11, 12, 13, 14, 15, and 16** are encompassed by **17**) with compounds **31** under the conditions suitable for the formation of compounds **I**. The conditions and methods discussed in Scheme 1 above for the synthesis of mono-protected diols **X** from alcohols **6** can be adapted for the synthesis of compounds **17**. Compounds **31**, wherein Y is a suitable leaving group as defined above, preferably an anhydride, an ester, or an amide group, are readily obtained commercially (*e.g.*, Aldrich Chemical Co. Milwaukee WI) or by well known synthetic methods. Compounds **I** are obtained by reacting compounds **31** with compounds **17** under the conditions suitable for alkyl-de-acyloxy substitution. (For a review, *See* Kharasch; Reinmuth, *Grignard Reactions of Nonmetallic Substances*; Prentice Hall: Englewood Cliffs, NJ, 1954, pp. 561-562 and 846-908. In a preferred procedure, the conversion of anhydrides, carboxylic esters, or amides to ketones with organometallic compounds. In a particular procedure, anhydrides and carboxylic esters give ketones when treated using inverse addition of Grignard reagents at low temperature with the solvent HMPA. *See* Newman, *J. Org. Chem.* **1948**, *13*, 592; Huet; Empotz; Jubier *Tetrahedron* **1973**, *29*, 479; and *Comprehensive Organic Transformations*; VCH: New York, **1989**, pp. 685-686, 693-700. Ketones can also be prepare by the treatment of thioamides with organolithium compounds (alkyl or aryl). *See* Tominaga; Kohra; Hosomi *Tetrahedron Lett.* **1987**, *28*, 1529. Moreover, alkyllithium compounds have been used to give ketones from carboxylic esters. *See* Petrov; Kaplan; Tsir *J. Gen. Chem. USSR* **1962**, *32*, 691. The reaction must be carried out in a high-boiling solvent such as toluene. Di-substituted amides also can be used to synthesize ketones. See Evans J. Chem. Soc. 1956, 4691; and Wakefield *Organolithium Methods*; Academic Press: New York, **1988**, pp. 82-88.

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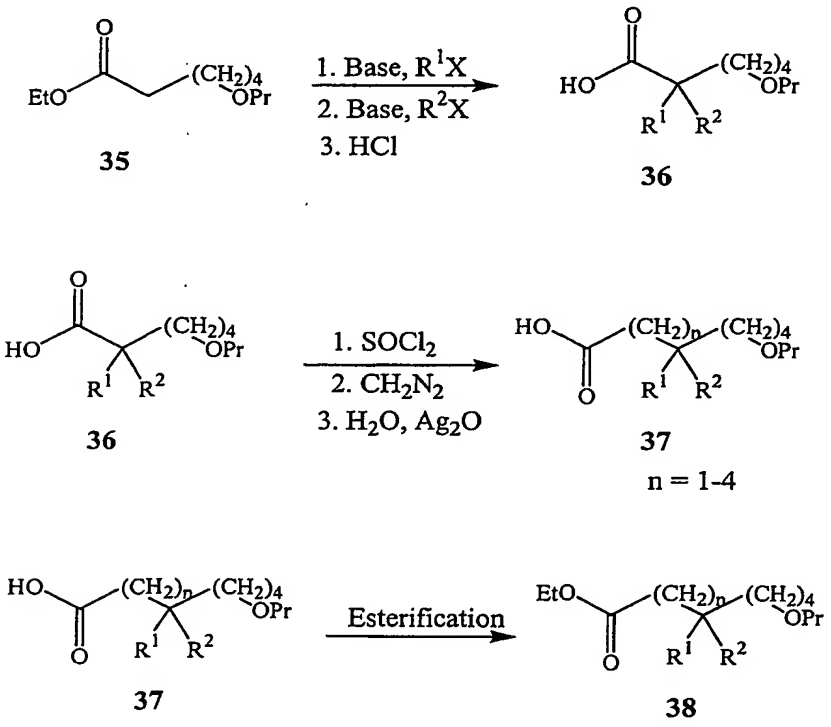
Scheme 9: Synthesis of Compounds of Formula II

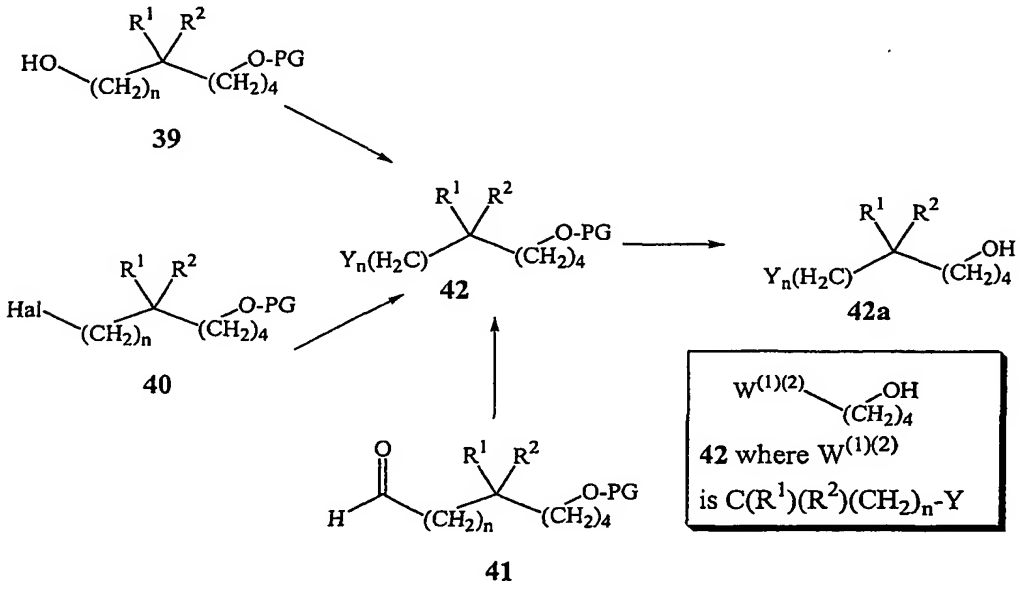


10 Scheme 9 illustrates the alpha disubstitution of an ester containing a terminal protected hydroxyl moiety. Compounds that contain strong electron withdrawing groups are easily converted to the corresponding enolates. These enolate ions can readilt attack an electrophile resulting in alpha substitution. *See Some Modern Methods of Organic Synthesis*, 3rd Ed.; Cambridge University Press: Cambridge, 1986, pp. 1-26, hereby
15 expressly incorporated herein by reference. The reaction is successful for primary and secondary alkyl, allylic, and benzylic. The use of polar aprotic solvents, *e.g.*, dimethylformamide or dimethylsulfoxide, are preferred. Phase transfer catalysts can also be

used. *See* Tundo *et al. J. Chem. Soc., Perkin Trans.* 1, **1987**, 2159, which is hereby expressly incorporated herein by reference.

The conversion to a carboxylic acid with an additional carbon is achieved by treating an acyl halide with diazomethane to generate an intermediate diazo ketone, which in the presence of water and silver oxide rearranges through a ketene intermediate to a carboxylic acid with an additional carbon aton **37**. If the reaction is done in an alcohol instead of water an ester is recovered. *See* Meier *et al. Angew. Chem. Int. Ed. Eng.* 1975, 14, 32-43, which is hereby expressly incorporated herein by reference. Alternatively, the carboxylic acid can be esterified by known techniques. The reaction can be repeated to generate methylene groups adjacent to the carboxylic acid.

Scheme 10: Synthesis of Compounds of Formula 42a which correspond to Compounds $W^{(1)(2)}$-$(CH_2)_4$-OH, wherein $W^{(1)(2)}$ is $C(R^1)(R^2)(CH_2)_nY$



Scheme 10 outlines methodology for the synthesis of protected alcohols **42a** wherein Y, R^1, R^2, Z, and m are defined as above. Protected alcohols **42a** correspond to compounds of the formula $W^{(1)(2)}$–Zm–OPG, wherein $W^{(1)(2)}$ is $C(R^1)(R^2)$–Y.

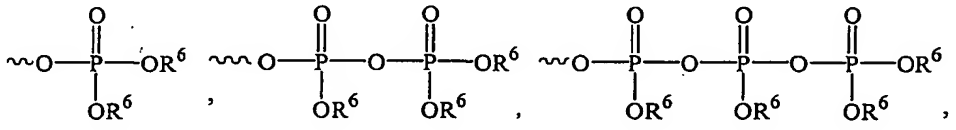
Protected alcohols **42**, wherein Y comprises a –COOH group, can be synthesized by oxidizing mono-protected diols **39** with an agent suitable for oxidizing a primary alcohol to a carboxylic acid (for a discussion see M. Hudlicky, *Oxidations in Organic Chemistry*, ACS Monograph 186, 1990, pp. 127-130, hereby expressly incorporated herein by reference).

Suitable oxidizing agents include, but are not limited to, pyridinium dichromate (Corey *et al.*,1979, *Tetrahedron Lett.* 399); manganese dioxide (Ahrens *et al.*,1967, *J. Heterocycl. Chem.* 4:625); sodium permanganate monohydrate (Menger *et al.*, 1981,*Tetrahedron Lett.* 22:1655); and potassium permanganate (Sam *et al.*,1972, *J. Am. Chem. Soc.* 94:4024), all of which citations are hereby expressly incorporated herein by reference. The preferred oxidizing reagent is pyridinium dichromate. In an alternative synthetic procedure, protected alcohols **42**, wherein Y comprises a –COOH group, can be synthesized by treatment of protected halo-alcohols **40**, wherein X is iodo, with CO or CO_2, as described in Bailey *et al.*,1990, *J. Org. Chem.* 55:5404 and Yanagisawa *et al.*,1994, *J. Am. Chem. Soc.* 116:6130, the two of which citations are hereby expressly incorporated herein by reference. Protected alcohols **42**, wherein Y comprises –C(O)OR^5, wherein R^5 is as defined above, can be synthesized by oxidation of mono-protected diols **39** in the presence of R^{5}OH (see generally, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 1196). An exemplary procedure for such an oxidation is described in Stevens *et al.*,1982, *Tetrahedron Lett.* 23:4647 (HOCl); Sundararaman *et al.*,1978, *Tetrahedron Lett.* 1627 (O_3/KOH); Wilson *et al.*,1982, *J. Org. Chem.* 47:1360 (*t*–BuOOH/Et_3N); and Williams *et al.*,1988, *Tetrahedron Lett.* 29:5087 (Br_2), the four of which citations are hereby expressly incorporated herein by reference. Preferably, protected alcohols **42**, wherein Y comprises a –C(O)OR^5 group are synthesized from the corresponding carboxylic acid (*i.e.*, **42**, wherein Y comprises –COOH) by esterification with R^{5}OH (*e.g., see* March, J., *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 393-394, hereby expressly incorporated herein by reference). In another alternative synthesis, protected alcohols **42**, wherein Y comprises –C(O)OR^5, can be prepared from protected halo-alcohols **40** by carbonylation with transition metal complexes (*see e.g.*, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 484-486; Urata *et al.*,1991, *Tetrahedron Lett.* 32:36, 4733); and Ogata *et al.*,1969, *J. Org. Chem.* 3985, the three of which citations are hereby expressly incorporated herein by reference).

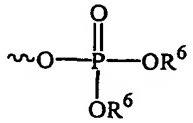
Protected alcohols **42**, wherein Y comprises –OC(O)R^5, wherein R^5 is as defined above, can be prepared by acylation of mono-protected diols **39** with a carboxylate equivalent such as an acyl halide (*i.e.*, R^{5}C(O)–Hal, wherein Hal is iodo, bromo, or chloro, *see e.g.*, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 392 and *Org. Synth. Coll.* Vol. III, Wiley, NY, pp. 142, 144, 167, and 187 (1955)) or an anhydride (*i.e.*, R^{5}C(O)–O–(O)CR^5, see *e.g.*, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 392-393 and *Org. Synth. Coll.* Vol. III, Wiley, NY, pp. 11, 127, 141, 169, 237, 281, 428, 432, 690, and 833 (1955),

all of which citations are incorporated herein by reference). Preferably, the reaction is conducted by adding a base to a solution comprising mono-protected diols **39**, a carboxylate equivalent, and an organic solvent, which solution is preferably maintained at a constant temperature within the range of 0°C to about room temperature. Solvents suitable for reacting mono-protected diols **39** with a carboxylate equivalent include, but are not limited to, dichloromethane, toluene, and ether, preferably dichloromethane. Suitable bases include, but are not limited to, hydroxide sources, such as sodium hydroxide, potassium hydroxide, sodium carbonate, or potassium carbonate; or an amine such as triethylamine, pyridine, or dimethylaminopyridine, amines are preferred. The progress of the reaction can be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance liquid chromatography and when substantially complete, the product can be isolated by workup and purified if desired.

Protected alcohols **42**, wherein Y comprises one of the following phosphate ester groups



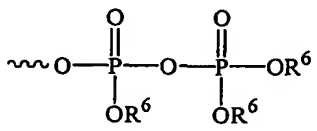
wherein R^6 is defined as above, can be prepared by phosphorylation of mono-protected diols **X** according to well-known methods (for a general reviews, see Corbridge *Phosphorus: An Outline of its Chemistry, Biochemistry, and Uses*, Studies in Inorganic Chemistry, 3rd ed., pp. 357-395 (1985); Ramirez *et al.*, 1978, *Acc. Chem. Res.* 11:239; and Kalckare *Biological Phosphorylations*, Prentice-Hall, New York (1969); J. B. Sweeny in *Comprehensive Organic Functional Group Transformations*, A.R. Katritzky, O. Meth-Cohn and C.W. Rees, Eds. Pergamon: Oxford, 1995, vol 2, pp. 104-109, the four of which are hereby expressly incorporated herein by reference). Protected alcohols **42** wherein Y comprises a monophosphate group of the formula:



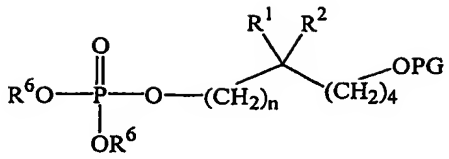
wherein R^6 is defined as above, can be prepared by treatment of mono-protected diol **39** with phosphorous oxychloride in a suitable solvent, such as xylene or toluene, at a constant

temperature within the range of about 100°C to about 150°C for about 2 hours to about 24 hours. After the reaction is deemed substantially complete, by using an appropriate analytical method, the reaction mixture is hydrolyzed with R^6–OH. Suitable procedures are referenced in Houben-Weyl, Methoden der Organische Chemie, Georg Thieme Verlag Stuttgart 1964, vol. XII/2, pp. 143-210 and 872-879, hereby expressly incorporated herein by reference. Alternatively, when both R^6 are hydrogen, can be synthesized by reacting mono-protected diols **X** with silyl polyphosphate (Okamoto *et al.*, 1985, *Bull Chem. Soc. Jpn.* 58:3393, hereby expressly incorporated herein by reference) or by hydrogenolysis of their benzyl or phenyl esters (Chen *et al.*, 1998, *J. Org. Chem.* 63:6511, incorporated herein by reference). In another alternative procedure, when R^6 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl, the monophosphate esters can be prepared by reacting mono-protected diols **39** with appropriately substituted phophoramidites followed by oxidation of the intermediate with *m*-chloroperbenzoic acid (Yu *et al.*, 1988, *Tetrahedron Lett.* 29:979, incorporated herein by reference) or by reacting mono-protected diols **39** with dialkyl or diaryl substituted phosphorochloridates (Pop, *et al*, 1997, *Org. Prep. and Proc. Int.* 29:341, incorporated herein by reference). The phosphoramidites are commercially available (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or readily prepared according to literature procedures (*see e.g.*, Uhlmann *et al.* 1986, *Tetrahedron Lett.* 27:1023 and Tanaka *et al.*, 1988, *Tetrahedron Lett.* 29:199, both of which are incorporated herein by reference). The phosphorochloridates are also commercially available (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or prepared according to literature methods (*e.g.*, Gajda *et al*, 1995, *Synthesis* 25:4099. In still another alternative synthesis, protected alcohols **42**, wherein Y comprises a monophosphate group and R^6 is alkyl or aryl, can be prepared by reacting $IP^+(OR^6)_3$ with mono-protected diols **39** according to the procedure described in Stowell *et al.*, 1995, *Tetrahedron Lett.* 36:11, 1825 or by alkylation of protected halo alcohols **40** with the appropriate dialkyl or diaryl phosphates (*see e.g.*, Okamoto, 1985, *Bull Chem. Soc. Jpn.* 58:3393, incorporated herein by reference).

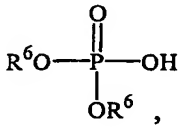
Protected alcohols **42** wherein Y comprises a diphosphate group of the formula



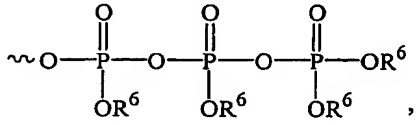
wherein R^6 is defined as above, can be synthesized by reacting the above-discussed monophosphates of the formula:



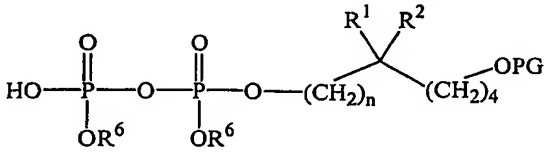
with a phosphate of the formula



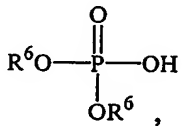
(commercially available, *e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin), in the presence of carbodiimide such as dicyclohexylcarbodiimide, as described in Houben-Weyl, *Methoden der Organische Chemie*, Georg Thieme Verlag Stuttgart 1964, vol. XII/2, pp. 881-885. In the same fashion, protected alcohols **42**, wherein Y comprises a triphosphate group of the formula:



can be synthesized by reacting the above-discussed diphosphate protected alcohols, of the formula:



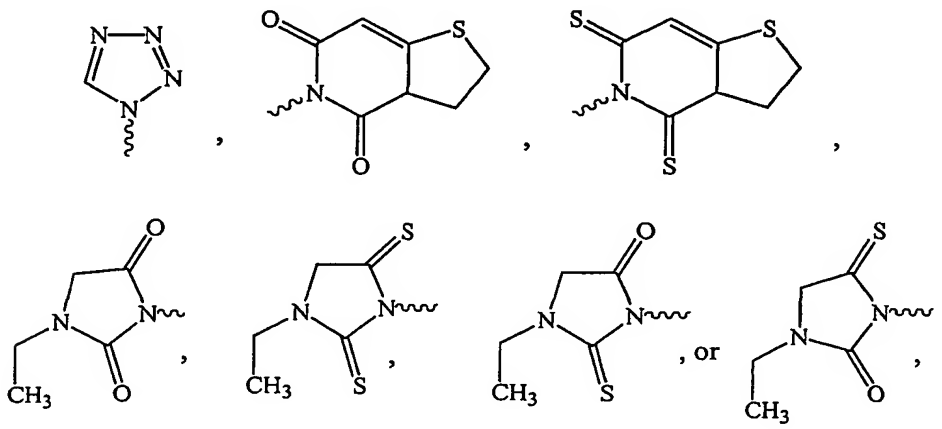
with a phosphate of the formula:



as described above. Alternatively, when R^6 is H, protected alcohols **42** wherein Y comprises the triphosphate group, can be prepared by reacting mono-protected diols **39** with salicyl phosphorochloridite and then pyrophosphate and subsequent cleavage of the adduct

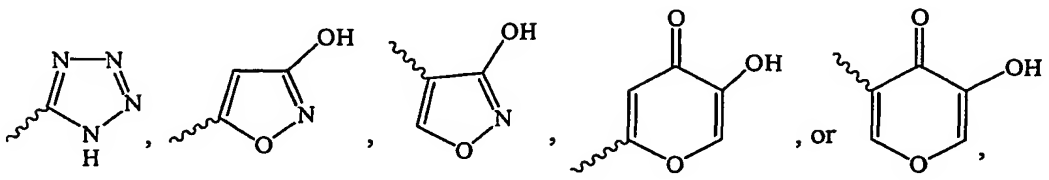
thus obtained with iodine in pyridine as described in Ludwig *et al.*, 1989, *J. Org. Chem.* 54:631, incorporated herein by reference.

Protected alcohols **42**, wherein Y is $-SO_3H$ or a heterocyclic group selected from the group consisting of:



can be prepared by halide displacement from protected halo-alcohols **40**. Thus, when Y is $-SO_3H$, protected alcohols **42** can by synthesized by reacting protected halo-alcohols **40** with sodium sulfite as described in Gilbert *Sulfonation and Related Reactions*; Wiley: New York, 1965, pp. 136-148 and pp. 161-163; *Org. Synth. Coll.* Vol. II, Wiley, NY, 558, 564 (1943); and *Org. Synth. Coll.* Vol. IV, Wiley, NY, 529 (1963), all three of which are incorporated herein by reference. When Y is one of the above-mentioned heterocycles, protected alcohols **42** can be prepared by reacting protected halo-alcohols **40** with the corresponding heterocycle in the presence of a base. The heterocycles are available commercially (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or prepared by well-known synthetic methods (see the procedures described in Ware, 1950, *Chem. Rev.* 46:403-470, incorporated herein by reference). Preferably, the reaction is conducted by stirring a mixture comprising **40**, the heterocycle, and a solvent at a constant temperature within the range of about room temperature to about 100°C, preferably within the range of about 50°C to about 70°C for about 10 to about 48 hours. Suitable bases include hydroxide bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, or potassium carbonate. Preferably, the solvent used in forming protected alcohols **42** is selected from dimethylformamide; formamide; dimethyl sulfoxide; alcohols, such as methanol or ethanol; and mixtures thereof. The progress of the reaction can be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance liquid chromatography and when substantially complete, the product can be isolated by workup and purified if desired.

Protected alcohols **42**, wherein Y is a heteroaryl ring selected from

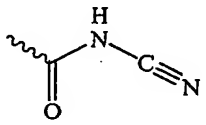


can be prepared by metallating the suitable heteroaryl ring then reacting the resulting metallated heteroaryl ring with protected halo-alcohols **40** (for a review, see Katritzky *Handbook of Heterocyclic Chemistry*, Pergamon Press: Oxford 1985). The heteroaryl rings are available commercially or prepared by well-known synthetic methods (*see e.g.*, Joule *et al., Heterocyclic Chemistry*, 3rd ed., 1995; De Sarlo *et al.*, 1971, *J. Chem. Soc. (C)* 86; Oster *et al.*, 1983, *J. Org. Chem.* 48:4307; Iwai *et al.*, 1966, *Chem. Pharm. Bull.* 14:1277; and United States Patent No. 3,152,148, all of which citations are incorporated herein by reference). As used herein, the term "metallating" means the forming of a carbon-metal bond, which bond may be substantially ionic in character. Metallation can be accomplished by adding about 2 equivalents of strong organometallic base, preferably with a pK_a of about 25 or more, more preferably with a pK_a of greater than about 35, to a mixture comprising a suitable organic solvent and the heterocycle. Two equivalents of base are required: one equivalent of the base deprotonates the –OH group or the –NH group, and the second equivalent metallates the heteroaryl ring. Alternatively, the hydroxy group of the heteroaryl ring can be protected with a base-stable, acid-labile protecting group as described in Greene, T.W., *Protective Groups in Organic Synthesis*, 3rd edition 17-237 (1999), hereby expressly incorporated herein by reference. Where the hydroxy group is protected, only one equivalent of base is required. Examples of suitable base-stable, acid-labile hydroxyl-protecting groups, include but are not limited to, ethers, such as methyl, methoxy methyl, methylthiomethyl, methoxyethoxymethyl, *bis*(2-chloroethoxy)methyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahyrofuranyl, tetrahydrothiofuranyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, *t*-butyl, allyl, benzyl, *o*-nitrobenzyl, triphenylmethyl, α-naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, 9-(9-phenyl-10-oxo)anthranyl, trimethylsilyl, isopropyldimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl; and esters, such as pivaloate, adamantoate, and 2,4,6-trimethylbenzoate. Ethers are preferred, particularly straight chain ethers, such as methyl ether, methoxymethyl ether, methylthiomethyl ether, methoxyethoxymethyl ether, *bis*(2-chloroethoxy)methyl ether. Preferably, the pK_a of the base is higher than the pK_a of the

proton of the heterocycle to be deprotonated. For a listing of pK_as for various heteroaryl rings, see Fraser *et al.*, 1985, *Can. J. Chem.* 63:3505, incorporated herein by reference. Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*–butyllithium, *tert*–butyllithium, *sec*–butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium hydride and potassium hydride. If desired, the organometallic base can be activated with a complexing agent, such as *N,N,N',N'*–tetramethylethylenediamine or hexamethylphosphoramide (1970, *J. Am. Chem. Soc.* 92:4664, hereby expressly incorporated herein by reference). Solvents suitable for synthesizing protected alcohols **42**, wherein Y is a heteroaryl ring include, but are not limited to, diethyl ether; tetrahydrofuran; and hydrocarbons, such as pentane. Generally, metallation occurs alpha to the heteroatom due to the inductive effect of the heteroatom, however, modification of conditions, such as the identity of the base and solvents, order of reagent addition, reagent addition times, and reaction and addition temperatures can be modified by one of skill in the art to achieve the desired metallation position (*see e.g.*, Joule *et al., Heterocyclic Chemistry*, 3rd ed., 1995, pp. 30-42, hereby expressly incorporated herein by reference) Alternatively, the position of metallation can be controlled by use of a halogenated heteroaryl group, wherein the halogen is located on the position of the heteroaryl ring where metallation is desired (*see e.g.*, Joule *et al., Heterocyclic Chemistry*, 3rd ed., 1995, p. 33 and Saulnier *et al.*, 1982, *J. Org. Chem.* 47:757, the two of which citations are hereby expressly incorporated herein by reference). Halogenated heteroaryl groups are available commercially (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or can be prepared by well-known synthetic methods (*see e.g.*, Joule *et al., Heterocyclic Chemistry*, 3rd ed., 1995, pp. 78, 85, 122, 193, 234, 261, 280, 308, hereby expressly incorporated herein by reference). After metallation, the reaction mixture comprising the metallated heteroaryl ring is adjusted to within a temperature range of about 0°C to about room temperature and protected halo-alcohols **40** (diluted with a solvent or in undiluted form) are added, preferably at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. After addition of protected halo-alcohols **40**, the reaction mixture is stirred at a constant temperature within the range of about room temperature and about the solvent's boiling temperature and the reaction's progress can be monitored by the appropriate analytical technique, preferably thin-layer chromatography or high-performance liquid chromatography. After the reaction

is substantially complete, protected alcohols **42** can be isolated by workup and purification. It is to be understood that conditions, such as the identity of protected halo-alcohol **40**, the base, solvents, orders of reagent addition, times, and temperatures, can be modified by one of skill in the art to optimize the yield and selectivity. Exemplary procedures that can be used in such a transformation are described in Shirley *et al.*, 1995, *J. Org. Chem.* 20:225; Chadwick *et al.*, 1979, *J. Chem. Soc., Perkin Trans. 1* 2845; Rewcastle, 1993, *Adv. Het. Chem.* 56:208; Katritzky *et al.*, 1993, *Adv. Het. Chem.* 56:155; and Kessar *et al.*, 1997, *Chem. Rev.* 97:721.

When Y is



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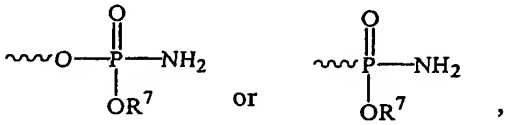
protected alcohols **42** can be prepared from their corresponding carboxylic acid derivatives (**42**, wherein Y is $-CO_2H$) as described in Belletire *et al*, 1988, *Synthetic Commun.* 18:2063 or from the corresponding acylchlorides (**42**, wherein Y is –CO–halo) as described in Skinner *et al.*, 1995, *J. Am. Chem. Soc.* 77:5440, both citations are incorporated herein by reference. The acylhalides can be prepared from the carboxylic acids by well known procedures such as those described in March, J., *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 437-438, hereby expressly incorporated herein by reference. When Y is



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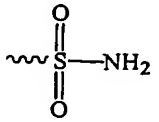
wherein R^7 is as defined above, protected alcohols **42** can be prepared by first reacting protected halo-alcohols **40** with a trialkyl phosphite according to the procedure described in Kosolapoff, 1951, *Org. React.* 6:273 followed by reacting the derived phosphonic diester with ammonia according to the procedure described in Smith *et al.*, 1957, *J. Org. Chem.* 22:265, incorporated herein by reference. When Y is



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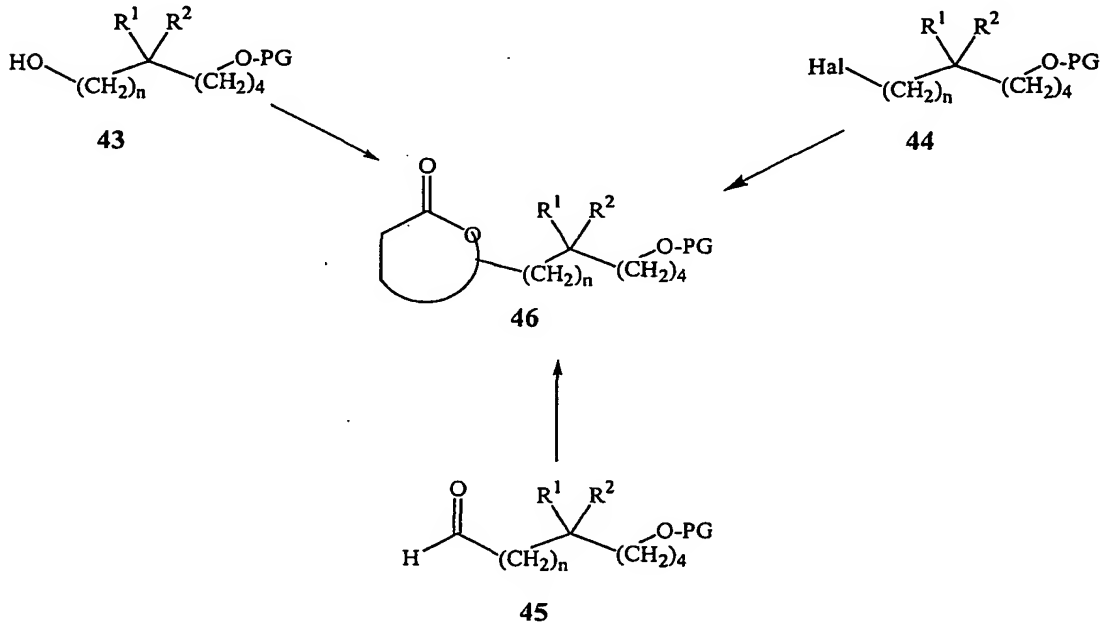
protected alcohols **42** can be prepared by reacting their sulphonic acid derivatives (*i.e.*, **42**, wherein Y is $-SO_3H$) with ammonia as described in Sianesi *et al.*, 1971, *Chem. Ber.* 104:1880 and Campagna *et al.*, 1994, *Farmaco, Ed. Sci.* 49:653, both of which citations are incorporated herein by reference).

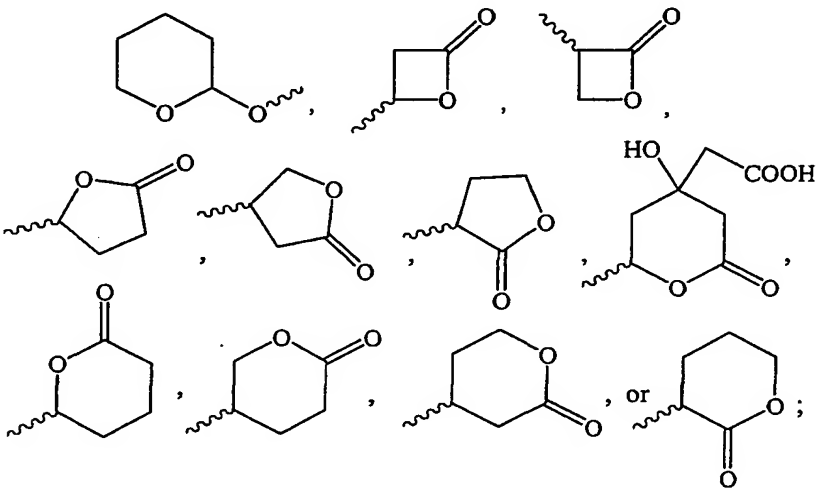
Scheme 11: Synthesis of Compounds of Formula 46 which correspond to Compounds $W^{(1)(2)}$-$(CH_2)_4$-OH, wherein $W^{(1)(2)}$ is $C(R^1)(R^2)(CH_2)_4$-Lactone



As further illustrated in Scheme 11, protected alcohols **42** can be deprotected providing alcohols **42a**. The deprotection method depends on the identity of the alcohol-protecting group, *see e.g.*, the procedures listed in Greene, T.W., *Protective Groups in Organic Synthesis*, 3rd edition 17-237 (1999), particularly see pages 48-49, incorporated herein by reference. One of skill in the art will readily be able to choose the appropriate deprotection procedure. When the alcohol is protected as an ether function (*e.g.*, methoxymethyl ether), the alcohol is preferably deprotected with aqueous or alcoholic acid. Suitable deprotection reagents include, but are not limited to, aqueous hydrochloric acid, *p*-toluenesulfonic acid in methanol, pyridinium-*p*-toluenesulfonate in ethanol, Amberlyst H–15 in methanol, boric acid in ethylene-glycol-monoethylether, acetic acid in a water–tetrahydrofuran mixture, aqueous hydrochloric acid is preferred. Examples of such procedures are described, respectively, in Bernady *et al.*, 1979, *J. Org. Chem.* 44:1438; Miyashita *et al.*, 1977, *J. Org. Chem.* 42:3772; Johnston *et al.*, 1988, *Synthesis* 393; Bongini *et al.*, 1979, *Synthesis* 618; and Hoyer *et al.*, 1986, *Synthesis* 655; Gigg *et al.*, 1967, *J. Chem.*

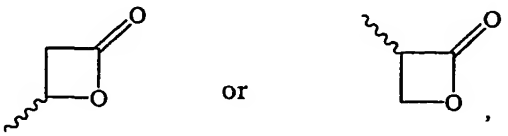
Soc. C, 431; and Corey *et al.*, 1978, *J. Am. Chem. Soc.* 100:1942, all of which are incorporated herein by reference.

Scheme 11 depicts the synthesis of protected lactone alcohols **46** and lactone. Compound **46** corresponds to compounds of the formula $W^{(1)(2)}$–Zm–OPG and , wherein $W^{(1)(2)}$ is a lactone group selected from:



Protected lactone alcohols **46** can be prepared from compounds of the formula **46**, **45**, or **44** by using well-known condensation reactions and variations of the Michael reaction. Methods for the synthesis of lactones are disclosed in Multzer in *Comprehensive Organic Functional Group Transformations*, A.R. Katritzky, O. Meth-Cohn and C.W. Rees, Eds. Pergamon: Oxford, 1995, vol 5, pp. 161-173, incorporated herein by reference. Mono-protected diols **43**, electrophilic protected alcohols **44**, and aldehydes **45** are readily available ether commercially (*e.g.*, Aldrich Chemical Co., Milwaukee, WI) or by well known synthetic procedures.

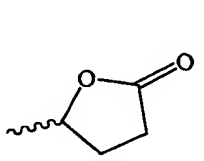
When $W^{(1)(2)}$ is a beta-lactone group of the formula:



3-beta-lactone 4-beta-lactone

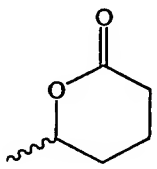
protected lactone alcohols **46** can be prepared from aldehydes **45** and electrophilic protected alcohols **44**, respectively, by a one-pot-addition-lactonization according to the procedure of Masamune *et al.*, 1976, *J. Am. Chem. Soc.* 98:7874 and Danheiser *et al.*, 1991, *J. Org. Chem.*

56:1176, both of which are incorporated herein by reference. This one-pot-addition-lactonization methodology has been reviewed by Multzer in *Comprehensive Organic Functional Group Transformations*, A.R. Katritzky, O. Meth-Cohn and C.W. Rees, Eds. Pergamon: Oxford, 1995, vol 5, pp. 161, incorporated herein by reference When $W^{(1)(2)}$ is a gamma- or delta-lactone group of the formula:



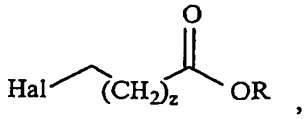
gamma-lactone

or



delta-lactone

protected lactone alcohols **46** can be prepared from aldehydes **45** according to well known synthetic methodology. For example, the methodology described in Masuyama *et al.*, 2000, *J. Org. Chem.* 65:494; Eisch *et al.*, 1978, *J. Organo. Met. Chem. C8* 160; Eaton *et al.*, 1947, *J. Org. Chem.* 37:1947; Yunker *et al.*, 1978, *Tetrahedron Lett.* 4651; Bhanot *et al.*, 1977, *J. Org. Chem.* 42:1623; Ehlinger *et al.*, 1980, *J. Am. Chem. Soc.* 102:5004; and Raunio *et al.*, 1957, *J. Org. Chem.* 22:570, all of which citations are incorporated herein by reference. For instance, as described in Masuyama *et al.*, 2000, *J. Org. Chem.* 65:494, aldehydes **45** can be treated with about 1 equivalent of a strong organometallic base, preferably with a pK_a of about 25 or more, more preferably with a pK_a of greater than about 35, in a suitable organic solvent to give a reaction mixture. Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*–butyllithium, *tert*–butyllithium, *sec*–butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium hydride and potassium hydride, preferably lithium tetramethylpiperidide. Suitable solvents include, but are not limited to, diethyl ether and tetrahydrofuran. The reaction-mixture temperature is adjusted to within the range of about 0°C to about 100°C, preferably about room temperature to about 50°C, and a halide of the formula:



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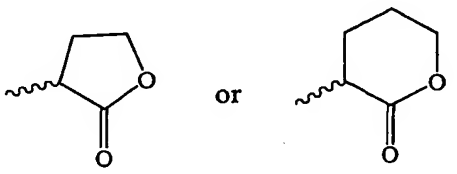
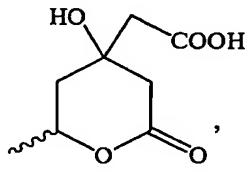
wherein z is 1 or 2 (diluted with a solvent or in undiluted form) is added. The reaction mixture is stirred for a period of about 2 hours to about 48 hours, preferably about 5 to about 10 hours, during which time the reaction's progress can be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance liquid chromatography. When the reaction is deemed substantially complete, protected lactone alcohols **46** can be isolated by workup and purified if desired. When $W^{(1)(2)}$ is a gamma- or delta-lactone group of the formula:



gamma-lactone delta-lactone

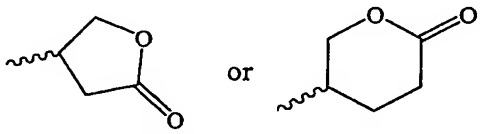
protected lactone alcohols **46** can be synthesized by deprotonating the corresponding lactone with a strong base providing the lactone enolate and reacting the enolate with electrophilic protected alcohols **44** (for a detailed discussion of enolate formation of active methylene compounds such as lactones, see House *Modern Synthetic Reactions*; W. A. Benjamin, Inc. Philippines 1972 pp. 492-570, and for a discussion of reaction of lactone enolates with electrophiles such as carbonyl compounds, see March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 944-945, both of which are incorporated herein by reference). Lactone-enolate formation can be accomplished by adding about 1 equivalent of a strong organometallic base, preferably with a pK_a of about 25 or more, more preferably with a pK_a of greater than about 35, to a mixture comprising a suitable organic solvent and the lactone. Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*–butyllithium, *tert*–butyllithium, *sec*–butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium hydride and potassium hydride, preferably lithium tetramethylpiperidide. Solvents suitable for lactone-enolate formation include, but are not limited to, diethyl ether and tetrahydrofuran. After enolate formation, the reaction-mixture temperature is adjusted to within the range of about –78°C to about room temperature, preferably about –50°C to about 0°C, and electrophilic protected alcohols **44** (diluted with a solvent or in undiluted form) are added, preferably at a rate such that the reaction-mixture temperature remains within about

one to two degrees of the initial reaction-mixture temperature. The reaction mixture is stirred for a period of about 15 minutes to about 5 hours, during which time the reaction's progress can be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance liquid chromatography. When the reaction is deemed substantially complete, protected lactone alcohols **46** can be isolated by workup and purified if desired. When $W^{(1)(2)}$ is a lactone group group of the formula:



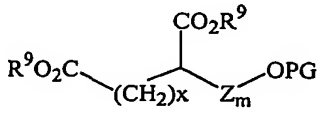
protected lactone alcohols **46** can be prepared from aldehydes **45** according to the procedure described in United States Patent No. 4,622,338, hereby expressly incorporated herein by reference.

When $W^{(1)(2)}$ is a gamma- or delta-lactone group of the formula:



gamma-lactone delta-lactone

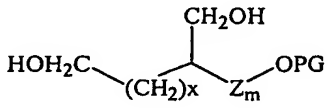
protected lactone alcohols **46** can be prepared according to a three step sequence. The first step comprises base-mediated reaction of electrophilic protected alcohols **44** with succinic acid esters (*i.e.*, $R^9O_2CCH_2CH_2CO_2R^9$, wherein R^9 is alkyl) or glutaric acid esters (*i.e.*, $R^9O_2CCH_2CH_2CH_2CO_2R^9$, wherein R^9 is alkyl) providing a diester intermediate of the formula **44i**:



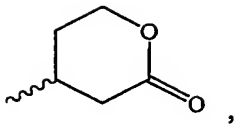
44i

wherein x is 1 or 2 depending on whether the gamma or delta lactone group is desired. The reaction can be performed by adding about 1 equivalent of a strong organometallic base, preferably with a pK_a of about 25 or more, more preferably with a pK_a of greater than about 35, to a mixture comprising a suitable organic solvent and the succinic or glutaric acid ester.

Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*–butyllithium, *tert*–butyllithium, *sec*–butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium hydride and potassium hydride, preferably lithium tetramethylpiperidide. Suitable solvents include, but are not limited to, diethyl ether and tetrahydrofuran. After enolate formation, the reaction-mixture temperature is adjusted to within the range of about –78°C to about room temperature, preferably about –50°C to about 0°C, and electrophilic protected alcohols **44** (diluted with a solvent or in undiluted form) are added, preferably at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. The reaction mixture is stirred for a period of about 15 minutes to about 5 hours, during which time the reaction's progress can be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance liquid chromatography. When the reaction is deemed substantially complete, the diester intermediate be isolated by workup and purified if desired. In the second step, the intermediate diester can be reduced, with a hydride reducing agent, to yield a diol:

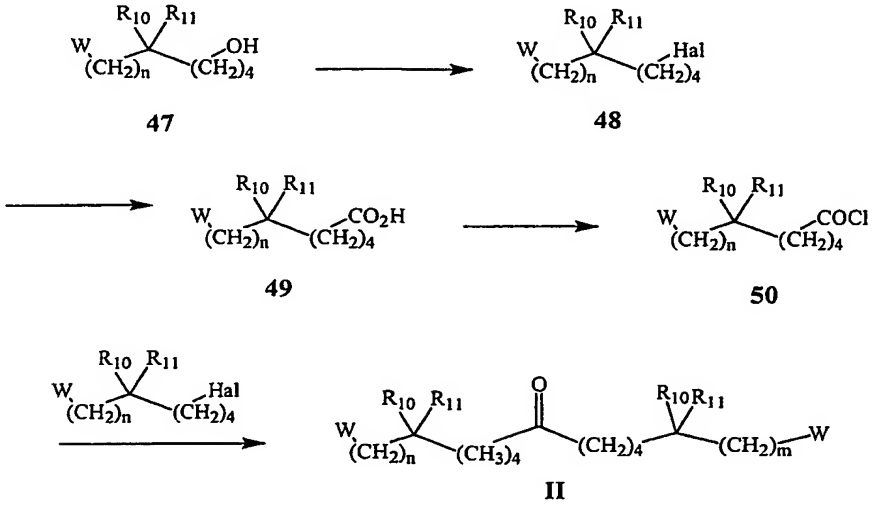


The reduction can be performed according to the procedures referenced in March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 1214, incorporated herein by reference). Suitable reducing agents include, but are not limited to, lithium aluminum hydride, diisobutylaluminum hydride, sodium borohydride, and lithium borohydride). In the third step, the diol can be oxidatively cyclized with $RuH_2(PPh_3)_4$ to the product protected lactone alcohols **46** according to the procedure of Yoshikawa *et al.*, 1986, *J. Org. Chem.* 51:2034 and Yoshikawa *et al.*, 1983, *Tetrahedron Lett.* 26:2677, both of which citations are incorporated herein by reference. When $W^{(1)(2)}$ is a lactone group of the formula:



protected lactone alcohols **46** can be synthesized by reacting the Grignard salts of electrophilic protected alcohols **44**, where E is a halide, with 5,6-dihydro-2*H*-pyran-2-one, commercially available (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin), in the presence of catalytic amounts of a 1-dimethylaminoacetyl)pyrolidine-2yl)methyl-diarylphosphine-copper (I) iodide complex as described in Tomioka *et al.*, 1995, *Tetrahedron Lett.* 36:4275, incorporated herein by reference.

Scheme 12: Synthesis of Compounds of Formula II

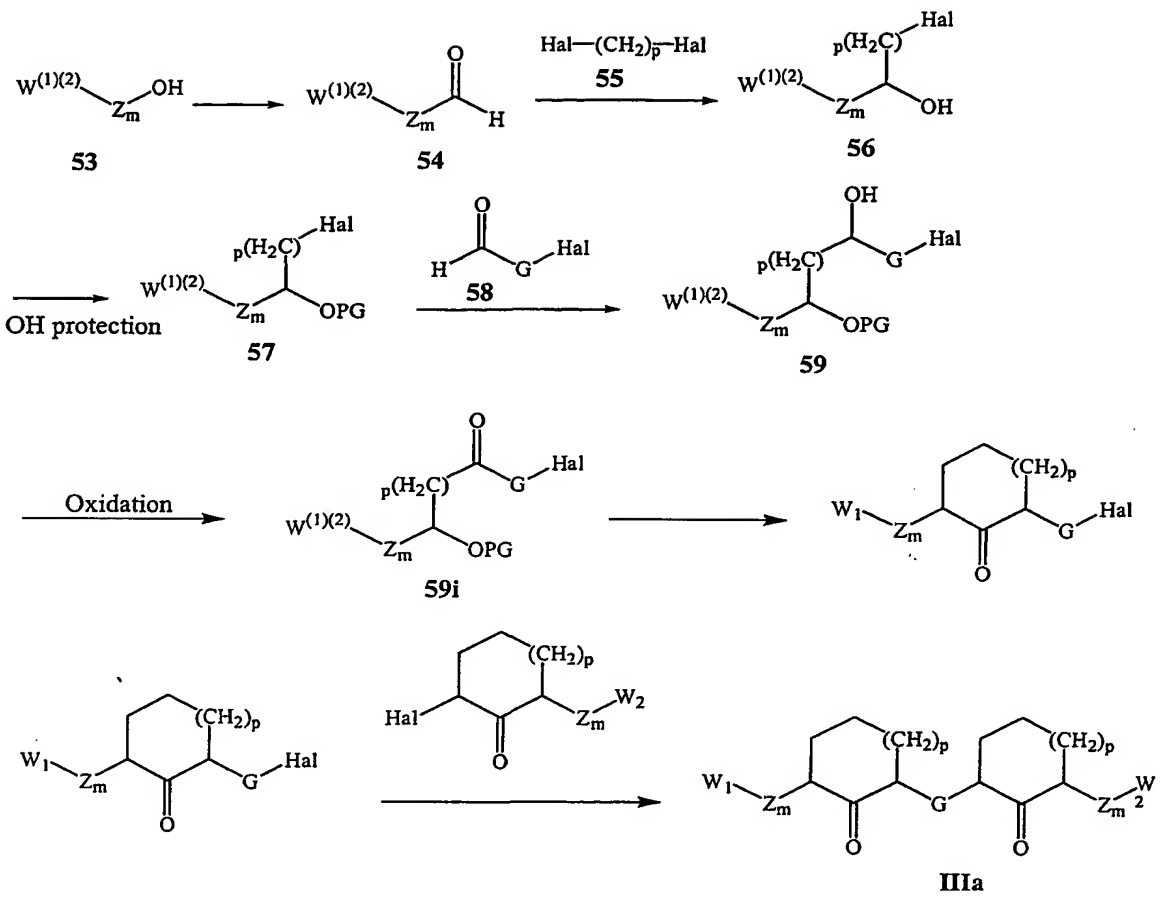


Scheme 12 illustrates the synthesis of ketone **II**. The alcohol **47** is intiallly converted to a halogen **48**. *See* Larock, *Comprehensive Organic Transformations*, VCH: New York, **1989**, pp. 360-362; all references disclosed therein are incorporated herein by reference. The halide **48** is then converted to a carboxylic acid **49** with subsequent conversion to a acyl halide **50**. *See* Larock, *Comprehensive Organic Transformations*, VCH: New York, **1989**, pp. 850-851, 855-856, 859-860, 977, 980, and 985; all references discloses therein are incorporated herein by reference. The acyl halide **50** is then coupled with the halide to afford compound **II**. *See* Rappoport, *The Chemistry of the Functional Groups, Supp. D*, pt. 2; Wiley: New York, **1983**; House, *Modern Synthetic Reactions*, 2nd

Ed. Benjamin: New York, **1972**, pp. 691-694, 734-765, which are incorporated herein by reference.

Scheme 13 depicts the synthesis of compounds **IIIa**, that is, compounds **III** where a double bond is not present in the ring. In the first step, compounds **53**, prepared as discussed in Schemes 1 to 6 above, can be converted to compounds **54** by standard oxidation of the primary alcohol to an aldehyde group. Such oxidations are described in M. Hudlicky, *Oxidations in Organic Chemistry*, ACS Monograph 186, 1990, pp. 114-127, hereby expressly incorporated herein by reference. In the next step Grignard reaction of **54** with **55** followed by standard OH protection gives **57**. Compounds **55** are commercially available (*e.g.*, from Aldrich Chemical Co. Milwakee, WI) or readily prepared by standard synthetic methodology. For exemplary procedures for Grignard reaction see March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 920-929, incorporated herein by reference. Similarly, in the next step, the Grignard salt of **57** is condensed with **58** to provide **59**. Next **59** is is oxidized and then cyclized to **60**. When p is one, exemplary cyclization procedures are found in Friedrichsen, W. in *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, W. C.; Scriven, E. F. V. Eds.; Pergamon Press: Oxford, 1996; Vol.2, p 351, and *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, W. C. Eds.; Pergamon Press: Oxford, 1986; Vol.3. When p is 0, cyclization procedures are found in Hepworth, J. D. in *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, W. C.; Scriven, E. F. V. Eds.; Pergamon Press: Oxford, 1996; Vol.5, p 351 and *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, W. C. Eds.; Pergamon Press: Oxford, 1986; Vol.3, all of which citations are hereby expressly incorporated herein by reference.

Scheme 13: Synthesis of Compounds III



The hydroxy ketone is subjected to cyclization, as described in the above Hepworth, J. D. in *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, W. C.; Scriven, E. F. V. Eds.; Pergamon Press: Oxford, 1996; Vol.5, p 386. For compounds **III** where $W^{(1)(2)}$ is $HO(CH_2)_n$-R^1R^2: The hydroxy group is first deprotected as described in Greene, T.W., *Protective Groups in Organic Synthesis*, 3rd edition(1999). For other structures, where Y is a group such as an acid, aldehydes, *etc.*, protection is needed (acids as esters, preferably pivaloyl, aldehydes as silyl derivatives such as TIPS, stable in both basic and acidic conditions). When $W^{(1)(2)}$ is a Lactone it can be introduced as discussed in Scheme 3 above. The compounds are then coupled to afford compound of the formula **IIIa**.

The reactions are performed under similar conditions for substituted cyclic compounds. After the formation of the mono-cyclic compounds, they are *in situ* reacted with electrophiles (*e.g.*, MeI) at temperatures between –40 °C to +60 °C, for a reaction time of 1 hr to 5 days. In addition, ing double bonds can be selectively added or reduced or

otherwise manipulated by well known synthetic methods to give compounds **III** having one or two selectively-placed double bonds (*i.e.*, the double bond(s) can be positioned in the desired location within the ring), for example, the methods disclosed in March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 771-780, incorporated herein by reference.

4.3. Therapeutic Uses of Compounds or Compositions of the Invention

In accordance with the invention, a compound of the invention or a composition of the invention, comprising a compound of the invention and a pharmaceutically acceptable vehicle, is administered to a patient, preferably a human, with or at risk of cardiovascular disease, a dyslipidemia, a dyslipoproteinemia, a disorder of glucose metabolism, Alzheimer's Disease, Syndrome X, a PPAR-associated disorder, septicemia, a thrombotic disorder, obesity, pancreatitis, hypertension, a renal disease, cancer, inflammation, or impotence. In one embodiment, "treatment" or "treating" refers to an amelioration of a disease or disorder, or at least one discernible symptom thereof. In another embodiment, "treatment" or "treating" refers to inhibiting the progression of a disease or disorder, either physically, *e.g.*, stabilization of a discernible symptom, physiologically, *e.g.*, stabilization of a physical parameter, or both.

In certain embodiments, the compounds of the invention or the compositions of the invention are administered to a patient, preferably a human, as a preventative measure against such diseases. As used herein, "prevention" or "preventing" refers to a reduction of the risk of acquiring a given disease or disorder. In a preferred mode of the embodiment, the compositions of the present invention are administered as a preventative measure to a patient, preferably a human having a genetic predisposition to a cardiovascular disease, a dyslipidemia, a dyslipoproteinemia, a disorder of glucose metabolism, Alzheimer's Disease, Syndrome X, a PPAR-associated disorder, septicemia, a thrombotic disorder, obesity, pancreatitis, hypertension, a renal disease, cancer, inflammation, or impotence. Examples of such genetic predispositions include but are not limited to the ε4 allele of apolipoprotein E, which increases the likelihood of Alzheimer's Disease; a loss of function or null mutation in the lipoprotein lipase gene coding region or promoter (*e.g.*, mutations in the coding regions resulting in the substitutions D9N and N291S; for a review of genetic mutations in the lipoprotein lipase gene that increase the risk of cardiovascular diseases, dyslipidemias and dyslipoproteinemias, see Hayden and Ma, 1992, *Mol. Cell Biochem.* 113:171-176); and familial combined hyperlipidemia and familial hypercholesterolemia .

In another preferred mode of the embodiment, the compounds of the invention or compositions of the invention are administered as a preventative measure to a patient having a non-genetic predisposition to a cardiovascular disease, a dyslipidemia, a dyslipoproteinemia, a disorder of glucose metabolism, Alzheimer's Disease, Syndrome X, a PPAR-associated disorder, septicemia, a thrombotic disorder, obesity, pancreatitis, hypertension, a renal disease, cancer, inflammation, or impotence. Examples of such non-genetic predispositions include but are not limited to cardiac bypass surgery and percutaneous transluminal coronary angioplasty, which often lead to restenosis, an accelerated form of atherosclerosis; diabetes in women, which often leads to polycystic ovarian disease; and cardiovascular disease, which often leads to impotence. Accordingly, the compositions of the invention may be used for the prevention of one disease or disorder and concurrently treating another (*e.g.*, prevention of polycystic ovarian disease while treating diabetes; prevention of impotence while treating a cardiovascular disease).

4.3.1. Cardiovascular Diseases for Treatment or Prevention

The present invention provides methods for the treatment or prevention of a cardiovascular disease, comprising administering to a patient a therapeutically effective amount of a compound or a composition comprising a compound of the invention and a pharmaceutically acceptable vehicle. As used herein, the term "cardiovascular diseases" refers to diseases of the heart and circulatory system. These diseases are often associated with dyslipoproteinemias and/or dyslipidemias. Cardiovascular diseases which the compositions of the present invention are useful for preventing or treating include but are not limited to arteriosclerosis; atherosclerosis; stroke; ischemia; endothelium dysfunctions, in particular those dysfunctions affecting blood vessel elasticity; peripheral vascular disease; coronary heart disease; myocardial infarcation; cerebral infarction and restenosis.

4.3.2. Dyslipidemias for Treatment or Prevention

The present invention provides methods for the treatment or prevention of a dyslipidemia comprising administering to a patient a therapeutically effective amount of a compound or a composition comprising a compound of the invention and a pharmaceutically acceptable vehicle.

As used herein, the term "dyslipidemias" refers to disorders that lead to or are manifested by aberrant levels of circulating lipids. To the extent that levels of lipids in the blood are too high, the compositions of the invention are administered to a patient to restore

normal levels. Normal levels of lipids are reported in medical treatises known to those of skill in the art. For example, recommended blood levels of LDL, HDL, free triglycerides and others parameters relating to lipid metabolism can be found at the web site of the American Heart Association and that of the National Cholesterol Education Program of the National Heart, Lung and Blood Institute (http://www.americanheart.org/cholesterol/about_level.html and http://www.nhlbi.nih.gov/health/ public/heart/chol/hbc_what.html, respectively). At the present time, the recommended level of HDL cholesterol in the blood is above 35 mg/dL; the recommended level of LDL cholesterol in the blood is below 130 mg/dL; the recommended LDL:HDL cholesterol ratio in the blood is below 5:1, ideally 3.5:1; and the recommended level of free triglycerides in the blood is less than 200 mg/dL.

Dyslipidemias which the compositions of the present invention are useful for preventing or treating include but are not limited to hyperlipidemia and low blood levels of high density lipoprotein (HDL) cholesterol. In certain embodiments, the hyperlipidemia for prevention or treatment by the compounds of the present invention is familial hypercholesterolemia; familial combined hyperlipidemia; reduced or deficient lipoprotein lipase levels or activity, including reductions or deficiencies resulting from lipoprotein lipase mutations; hypertriglyceridemia; hypercholesterolemia; high blood levels of ketone bodies (*e.g.* β-OH butyric acid); high blood levels of Lp(a) cholesterol; high blood levels of low density lipoprotein (LDL) cholesterol; high blood levels of very low density lipoprotein (VLDL) cholesterol and high blood levels of non-esterified fatty acids.

The present invention further provides methods for altering lipid metabolism in a patient, *e.g.*, reducing LDL in the blood of a patient, reducing free triglycerides in the blood of a patient, increasing the ratio of HDL to LDL in the blood of a patient, and inhibiting saponified and/or non-saponified fatty acid synthesis, said methods comprising administering to the patient a compound or a composition comprising a compound of the invention in an amount effective alter lipid metabolism.

4.3.3. Dyslipoproteinemias for Treatment or Prevention

The present invention provides methods for the treatment or prevention of a dyslipoproteinemia comprising administering to a patient a therapeutically effective amount of a compound or a composition comprising a compound of the invention and a pharmaceutically acceptable vehicle.

As used herein, the term "dyslipoproteinemias" refers to disorders that lead to or are manifested by aberrant levels of circulating lipoproteins. To the extent that levels of

lipoproteins in the blood are too high, the compositions of the invention are administered to a patient to restore normal levels. Conversely, to the extent that levels of lipoproteins in the blood are too low, the compositions of the invention are administered to a patient to restore normal levels. Normal levels of lipoproteins are reported in medical treatises known to those of skill in the art.

Dyslipoproteinemias which the compositions of the present invention are useful for preventing or treating include but are not limited to high blood levels of LDL; high blood levels of apolipoprotein B (apo B); high blood levels of Lp(a); high blood levels of apo(a); high blood levels of VLDL; low blood levels of HDL; reduced or deficient lipoprotein lipase levels or activity, including reductions or deficiencies resulting from lipoprotein lipase mutations; hypoalphalipoproteinemia; lipoprotein abnormalities associated with diabetes; lipoprotein abnormalities associated with obesity; lipoprotein abnormalities associated with Alzheimer's Disease; and familial combined hyperlipidemia.

The present invention further provides methods for reducing apo C-II levels in the blood of a patient; reducing apo C-III levels in the blood of a patient; elevating the levels of HDL associated proteins, including but not limited to apo A-I, apo A-II, apo A-IV and apo E in the blood of a patient; elevating the levels of apo E in the blood of a patient, and promoting clearance of triglycerides from the blood of a patient, said methods comprising administering to the patient a compound or a composition comprising a compound of the invention in an amount effective to bring about said reduction, elevation or promotion, respectively.

4.3.4. Glucose Metabolism Disorders for Treatment or Prevention

The present invention provides methods for the treatment or prevention of a glucose metabolism disorder, comprising administering to a patient a therapeutically effective amount of a compound or a composition comprising a compound of the invention and a pharmaceutically acceptable vehicle. As used herein, the term "glucose metabolism disorders" refers to disorders that lead to or are manifested by aberrant glucose storage and/or utilization. To the extent that indicia of glucose metabolism (*i.e.*, blood insulin, blood glucose) are too high, the compositions of the invention are administered to a patient to restore normal levels. Conversely, to the extent that indicia of glucose metabolism are too low, the compositions of the invention are administered to a patient to restore normal levels. Normal indicia of glucose metabolism are reported in medical treatises known to those of skill in the art.

Glucose metabolism disorders which the compositions of the present invention are useful for preventing or treating include but are not limited to impaired glucose tolerance; insulin resistance; insulin resistance related breast, colon or prostate cancer; diabetes, including but not limited to non-insulin dependent diabetes mellitus (NIDDM), insulin dependent diabetes mellitus (IDDM), gestational diabetes mellitus (GDM), and maturity onset diabetes of the young (MODY); pancreatitis; hypertension; polycystic ovarian disease; and high levels of blood insulin and/or glucose.

The present invention further provides methods for altering glucose metabolism in a patient, for example to increase insulin sensitivity and/or oxygen consumption of a patient, said methods comprising administering to the patient a compound or a composition comprising a compound of the invention in an amount effective to alter glucose metabolism.

4.3.5. PPAR Associated Disorders for Treatment or Prevention

The present invention provides methods for the treatment or prevention of a PPAR-associated disorder, comprising administering to a patient a therapeutically effective amount of a compound or a composition comprising a compound of the invention and a pharmaceutically acceptable vehicle. As used herein, "treatment or prevention of PPAR associated disorders" encompasses treatment or prevention of rheumatoid arthritis; multiple sclerosis; psoriasis; inflammatory bowel diseases; breast; colon or prostate cancer; low levels of blood HDL; low levels of blood, lymph and/or cerebrospinal fluid apo E; low blood, lymph and/or cerebrospinal fluid levels of apo A-I; high levels of blood VLDL; high levels of blood LDL; high levels of blood triglyceride; high levels of blood apo B; high levels of blood apo C-III and reduced ratio of post-heparin hepatic lipase to lipoprotein lipase activity. HDL may be elevated in lymph and/or cerebral fluid.

4.3.6. Renal Diseases for Treatment or Prevention

The present invention provides methods for the treatment or prevention of a renal disease, comprising administering to a patient a therapeutically effective amount of a compound or a composition comprising a compound of the invention and a pharmaceutically acceptable vehicle. Renal diseases that can be treated by the compounds of the present invention include glomerular diseases (including but not limited to acute and chronic glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, focal proliferative glomerulonephritis, glomerular lesions associated with systemic disease, such as systemic lupus erythematosus, Goodpasture's syndrome, multiple myeloma, diabetes, neoplasia, sickle cell disease, and chronic inflammatory diseases), tubular diseases

(including but not limited to acute tubular necrosis and acute renal failure, polycystic renal diseasemedullary sponge kidney, medullary cystic disease, nephrogenic diabetes, and renal tubular acidosis), tubulointerstitial diseases (including but not limited to pyelonephritis, drug and toxin induced tubulointerstitial nephritis, hypercalcemic nephropathy, and hypokalemic nephropathy) acute and rapidly progressive renal failure, chronic renal failure, nephrolithiasis, or tumors (including but not limited to renal cell carcinoma and nephroblastoma). In a most preferred embodiment, renal diseases that are treated by the compounds of the present invention are vascular diseases, including but not limited to hypertension, nephrosclerosis, microangiopathic hemolytic anemia, atheroembolic renal disease, diffuse cortical necrosis, and renal infarcts.

4.3.7. Cancers for Treatment or Prevention

The present invention provides methods for the treatment or prevention of cancer, comprising administering to a patient a therapeutically effective amount of a compound or a composition comprising a compound of the invention and a pharmaceutically acceptable vehicle. Cancers that can be treated or prevented by administering the compounds or the compositions of the invention include, but are not limited to, human sarcomas and carcinomas, *e.g.*, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, *e.g.*, acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenström's macroglobulinemia, and heavy chain disease. In a most preferred embodiment, cancers that are treated or prevented by administering the compounds of the

present invention are insulin resistance or Syndrome X related cancers, including but not limited to breast, prostate and colon cancer.

4.3.8. Other Diseases for Treatment or Prevention

The present invention provides methods for the treatment or prevention of Alzheimer's Disease, Syndrome X, septicemia, thrombotic disorders, obesity, pancreatitis, hypertension, inflammation, and impotence, comprising administering to a patient a therapeutically effective amount of a compound or a composition comprising a compound of the invention and a pharmaceutically acceptable vehicle.

As used herein, "treatment or prevention of Alzheimer's Disease" encompasses treatment or prevention of lipoprotein abnormalities associated with Alzheimer's Disease.

As used herein, "treatment or prevention of Syndrome X or Metabolic Syndrome" encompasses treatment or prevention of a symptom thereof, including but not limited to impaired glucose tolerance, hypertension and dyslipidemia/dyslipoproteinemia.

As used herein, "treatment or prevention of septicemia" encompasses treatment or prevention of septic shock.

As used herein, "treatment or prevention of thrombotic disorders" encompasses treatment or prevention of high blood levels of fibrinogen and promotion of fibrinolysis.

In addition to treating or preventing obesity, the compositions of the invention can be administered to an individual to promote weight reduction of the individual.

4.4. Surgical Uses

Cardiovascular diseases such as atherosclerosis often require surgical procedures such as angioplasty. Angioplasty is often accompanied by the placement of a reinforcing a metallic tube-shaped structure known as a "stent" into a damaged coronary artery. For more serious conditions, open heart surgery such as coronary bypass surgery may be required. These surgical procedures entail using invasive surgical devices and/or implants, and are associated with a high risk of restenosis and thrombosis. Accordingly, the compounds and compositions of the invention may be used as coatings on surgical devices (*e.g.*, catheters) and implants (*e.g.*, stents) to reduce the risk of restenosis and thrombosis associated with invasive procedures used in the treatment of cardiovascular diseases.

4.5. Veterinary and Livestock Uses

A composition of the invention can be administered to a non-human animal for a veterinary use for treating or preventing a disease or disorder disclosed herein.

In a specific embodiment, the non-human animal is a household pet. In another specific embodiment, the non-human animal is a livestock animal. In a preferred embodiment, the non-human animal is a mammal, most preferably a cow, horse, sheep, pig, cat, dog, mouse, rat, rabbit, or guinea pig. In another preferred embodiment, the non-human animal is a fowl species, most preferably a chicken, turkey, duck, goose, or quail.

In addition to veterinary uses, the compounds and compositions of the invention can be used to reduce the fat content of livestock to produce leaner meats. Alternatively, the compounds and compositions of the invention can be used to reduce the cholesterol content of eggs by administering the compounds to a chicken, quail, or duck hen. For non-human animal uses, the compounds and compositions of the invention can be administered via the animals' feed or orally as a drench composition.

4.6. Therapeutic/Prophylactic Administration and Compositions

Due to the activity of the compounds and compositions of the invention, they are useful in veterinary and human medicine. As described above, the compounds and compositions of the invention are useful for the treatment or prevention of cardiovascular diseases, dyslipidemias, dyslipoproteinemias, glucose metabolism disorders, Alzheimer's Disease, Syndrome X, PPAR-associated disorders, septicemia, thrombotic disorders, obesity, pancreatitis, hypertension, renal disease, cancer, inflammation, and impotence.

The invention provides methods of treatment and prophylaxis by administration to a patient of a therapeutically effective amount of a compound or a composition comprising a compound of the invention. The patient is an animal, including, but not limited, to an animal such a cow, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, guinea pig, *etc.*, and is more preferably a mammal, and most preferably a human.

The compounds and compositions of the invention, are preferably administered orally. The compounds and compositions of the invention may also be administered by any other convenient route, for example, by intravenous infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, *etc.*) and may be administered together with another biologically active agent. Administration can be systemic or local. Various delivery systems are known, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, capsules, *etc.*, and can be used to administer a compound of the invention. In certain embodiments, more than one compound of the invention is administered to a patient. Methods of administration include but are not

limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intranasal, intracerebral, intravaginal, transdermal, rectally, by inhalation, or topically, particularly to the ears, nose, eyes, or skin. The preferred mode of administration is left to the discretion of the practitioner, and will depend in-part upon the site of the medical condition. In most instances, administration will result in the release of the compounds of the invention into the bloodstream.

In specific embodiments, it may be desirable to administer one or more compounds of the invention locally to the area in need of treatment. This may be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. In one embodiment, administration can be by direct injection at the site (or former site) of an atherosclerotic plaque tissue.

In certain embodiments, for example, for the treatment of Alzheimer's Disease, it may be desirable to introduce one or more compounds of the invention into the central nervous system by any suitable route, including intraventricular, intrathecal and epidural injection. Intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or synthetic pulmonary surfactant. In certain embodiments, the compounds of the invention can be formulated as a suppository, with traditional binders and vehicles such as triglycerides.

In another embodiment, the compounds and compositions of the invention can be delivered in a vesicle, in particular a liposome (*see* Langer, 1990, *Science* 249:1527-1533; Treat *et al.*, in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; *see* generally *ibid.*).

In yet another embodiment, the compounds and compositions of the invention can be delivered in a controlled release system. In one embodiment, a pump may be used (*see* Langer, *supra*; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:201; Buchwald *et al.*, 1980, *Surgery* 88:507 Saudek *et al.*, 1989, *N. Engl. J. Med.* 321:574). In another embodiment, polymeric materials can be used (*see* Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability,

Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, 1983, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61; *see also* Levy *et al.*, 1985, *Science* 228:190; During *et al.*, 1989, *Ann. Neurol.* 25:351; Howard *et al.*, 1989, *J. Neurosurg.* 71:105). In yet another embodiment, a controlled-release system can be placed in proximity of the target area to be treated, *e.g.*, the liver, thus requiring only a fraction of the systemic dose (*see, e.g.*, Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)). Other controlled-release systems discussed in the review by Langer, 1990, *Science* 249:1527-1533) may be used.

The present compositions will contain a therapeutically effective amount of a compound of the invention, optionally more than one compound of the invention, preferably in purified form, together with a suitable amount of a pharmaceutically acceptable vehicle so as to provide the form for proper administration to the patient.

In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "vehicle" refers to a diluent, adjuvant, excipient, or carrier with which a compound of the invention is administered. Such pharmaceutical vehicles can be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical vehicles can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents may be used. When administered to a patient, the compounds and compositions of the invention and pharmaceutically acceptable vehicles are preferably sterile. Water is a preferred vehicle when the compound of the invention is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid vehicles, particularly for injectable solutions. Suitable pharmaceutical vehicles also include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

The present compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the pharmaceutically acceptable vehicle is a capsule

(see *e.g.*, U.S. Patent No. 5,698,155). Other examples of suitable pharmaceutical vehicles are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

In a preferred embodiment, the compounds and compositions of the invention are formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compounds and compositions of the invention for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the compositions may also include a solubilizing agent. Compositions for intravenous administration may optionally include a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the compound of the invention is to be administered by intravenous infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the compound of the invention is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

Compounds and compositions of the invention for oral delivery may be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs. Compounds and compositions of the invention for oral delivery can also be formulated in foods and food mixes. Orally administered compositions may contain one or more optionally agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions may be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compounds and compositions of the invention. In these later platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time delay material such as glycerol monostearate or glycerol stearate may also be used. Oral compositions can include standard vehicles such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, *etc.* Such vehicles are preferably of pharmaceutical grade.

The amount of a compound of the invention that will be effective in the treatment of a particular disorder or condition disclosed herein will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the compositions will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. However, suitable dosage ranges for oral administration are generally about 0.001 milligram to 200 milligrams of a compound of the invention per kilogram body weight. In specific preferred embodiments of the invention, the oral dose is 0.01 milligram to 70 milligrams per kilogram body weight, more preferably 0.1 milligram to 50 milligrams per kilogram body weight, more preferably 0.5 milligram to 20 milligrams per kilogram body weight, and yet more preferably 1 milligram to 10 milligrams per kilogram body weight. In a most preferred embodiment, the oral dose is 5 milligrams of a compound of the invention per kilogram body weight. The dosage amounts described herein refer to total amounts administered; that is, if more than one compound of the invention is administered, the preferred dosages correspond to the total amount of the compounds of the invention administered. Oral compositions preferably contain 10% to 95% active ingredient by weight.

Suitable dosage ranges for intravenous (i.v.) administration are 0.01 milligram to 100 milligrams per kilogram body weight, 0.1 milligram to 35 milligrams per kilogram body weight, and 1 milligram to 10 milligrams per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 pg/kg body weight to 1 mg/kg body weight. Suppositories generally contain 0.01 milligram to 50 milligrams of a compound of the invention per kilogram body weight and comprise active ingredient in the range of 0.5% to 10% by weight. Recommended dosages for intradermal, intramuscular, intraperitoneal, subcutaneous, epidural, sublingual, intracerebral, intravaginal, transdermal administration or administration by inhalation are in the range of 0.001 milligram to 200 milligrams per kilogram of body weight. Suitable doses of the compounds of the invention for topical administration are in the range of 0.001 milligram to 1 milligram, depending on the area to which the compound is administered. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems. Such animal models and systems are well known in the art.

The invention also provides pharmaceutical packs or kits comprising one or more containers filled with one or more compounds of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency

regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In a certain embodiment, the kit contains more than one compound of the invention. In another embodiment, the kit comprises a compound of the invention and another lipid-mediating compound, including but not limited to a statin, a thiazolidinedione, or a fibrate.

The compounds of the invention are preferably assayed *in vitro* and *in vivo*, for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays can be used to determine whether administration of a specific compound of the invention or a combination of compounds of the invention is preferred for lowering fatty acid synthesis. The compounds and compositions of the invention may also be demonstrated to be effective and safe using animal model systems.

Other methods will be known to the skilled artisan and are within the scope of the invention.

4.7. Combination Therapy

In certain embodiments of the present invention, the compounds and compositions of the invention can be used in combination therapy with at least one other therapeutic agent. The compound of the invention and the therapeutic agent can act additively or, more preferably, synergistically. In a preferred embodiment, a compound or a composition comprising a compound of the invention is administered concurrently with the administration of another therapeutic agent, which can be part of the same composition as the compound of the invention or a different composition. In another embodiment, a compound or a composition comprising a compound of the invention is administered prior or subsequent to administration of another therapeutic agent. As many of the disorders for which the compounds and compositions of the invention are useful in treating are chronic disorders, in one embodiment combination therapy involves alternating between administering a compound or a composition comprising a compound of the invention and a composition comprising another therapeutic agent, *e.g.*, to minimize the toxicity associated with a particular drug. The duration of administration of each drug or therapeutic agent can be, *e.g.*, one month, three months, six months, or a year. In certain embodiments, when a composition of the invention is administered concurrently with another therapeutic agent that potentially produces adverse side effects including but not limited to toxicity, the therapeutic agent can advantageously be administered at a dose that falls below the threshold at which the adverse side is elicited.

The present compositions can be administered together with a statin. Statins for use in combination with the compounds and compositions of the invention include but are not limited to atorvastatin, pravastatin, fluvastatin, lovastatin, simvastatin, and cerivastatin.

The present compositions can also be administered together with a PPAR agonist, for example a thiazolidinedione or a fibrate. Thiazolidinediones for use in combination with the compounds and compositions of the invention include but are not limited to 5-((4-(2-(methyl-2-pyridinylamino)ethoxy)phenyl)methyl)-2,4-thiazolidinedione, troglitazone, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, darglitazone, and rosiglitazone. Fibrates for use in combination with the compounds and compositions of the invention include but are not limited to gemfibrozil, fenofibrate, clofibrate, or ciprofibrate. As mentioned previously, a therapeutically effective amount of a fibrate or thiazolidinedione often has toxic side effects. Accordingly, in a preferred embodiment of the present invention, when a composition of the invention is administered in combination with a PPAR agonist, the dosage of the PPAR agonist is below that which is accompanied by toxic side effects.

The present compositions can also be administered together with a bile-acid-binding resin. Bile-acid-binding resins for use in combination with the compounds and compositions of the invention include but are not limited to cholestyramine and colestipol hydrochloride. The present compositions can also be administered together with niacin or nicotinic acid. The present compositions can also be administered together with a RXR agonist. RXR agonists for use in combination with the compounds of the invention include but are not limited to LG 100268, LGD 1069, 9-cis retinoic acid, 2-(1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-cyclopropyl)-pyridine-5-carboxylic acid, or 4-((3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)2-carbonyl)-benzoic acid. The present compositions can also be administered together with an anti-obesity drug. Anti-obesity drugs for use in combination with the compounds of the invention include but are not limited to β-adrenergic receptor agonists, preferably β-3 receptor agonists, fenfluramine, dexfenfluramine, sibutramine, bupropion, fluoxetine, and phentermine. The present compositions can also be administered together with a hormone. Hormones for use in combination with the compounds of the invention include but are not limited to thyroid hormone, estrogen and insulin. Preferred insulins include but are not limited to injectable insulin, transdermal insulin, inhaled insulin, or any combination thereof. As an alternative to insulin, an insulin derivative, secretagogue, sensitizer or mimetic may be used. Insulin secretagogues for use in combination with the compounds of

the invention include but are not limited to forskolin, dibutryl cAMP or isobutylmethylxanthine (IBMX).

The present compositions can also be administered together with a tyrophostine or an analog thereof. Tyrophostines for use in combination with the compounds of the invention include but are not limited to tryophostine 51.

The present compositions can also be administered together with sulfonylurea-based drugs. Sulfonylurea-based drugs for use in combination with the compounds of the invention include, but are not limited to, glisoxepid, glyburide, acetohexamide, chlorpropamide, glibornuride, tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide, and tolcyclamide. The present compositions can also be administered together with a biguanide. Biguanides for use in combination with the compounds of the invention include but are not limited to metformin, phenformin and buformin.

The present compositions can also be administered together with an α-glucosidase inhibitor. α-glucosidase inhibitors for use in combination with the compounds of the invention include but are not limited to acarbose and miglitol.

The present compositions can also be administered together with an apo A-I agonist. In one embodiment, the apo A-I agonist is the Milano form of apo A-I (apo A-IM). In a preferred mode of the embodiment, the apo A-IM for administration in conjunction with the compounds of the invention is produced by the method of U.S. Patent No. 5,721,114 to Abrahamsen. In a more preferred embodiment, the apo A-I agonist is a peptide agonist. In a preferred mode of the embodiment, the apo A-I peptide agonist for administration in conjunction with the compounds of the invention is a peptide of U.S. Patent No. 6,004,925 or 6,037,323 to Dasseux.

The present compositions can also be administered together with apolipoprotein E (apo E). In a preferred mode of the embodiment, the apoE for administration in conjunction with the compounds of the invention is produced by the method of U.S. Patent No. 5,834,596 to Ageland.

In yet other embodiments, the present compositions can be administered together with an HDL-raising drug; an HDL enhancer; or a regulator of the apolipoprotein A-I, apolipoprotein A-IV and/or apolipoprotein genes.

4.8. Combination Therapy with Cardiovascular Drugs

The present compositions can be administered together with a known cardiovascular drug. Cardiovascular drugs for use in combination with the compounds of the invention to

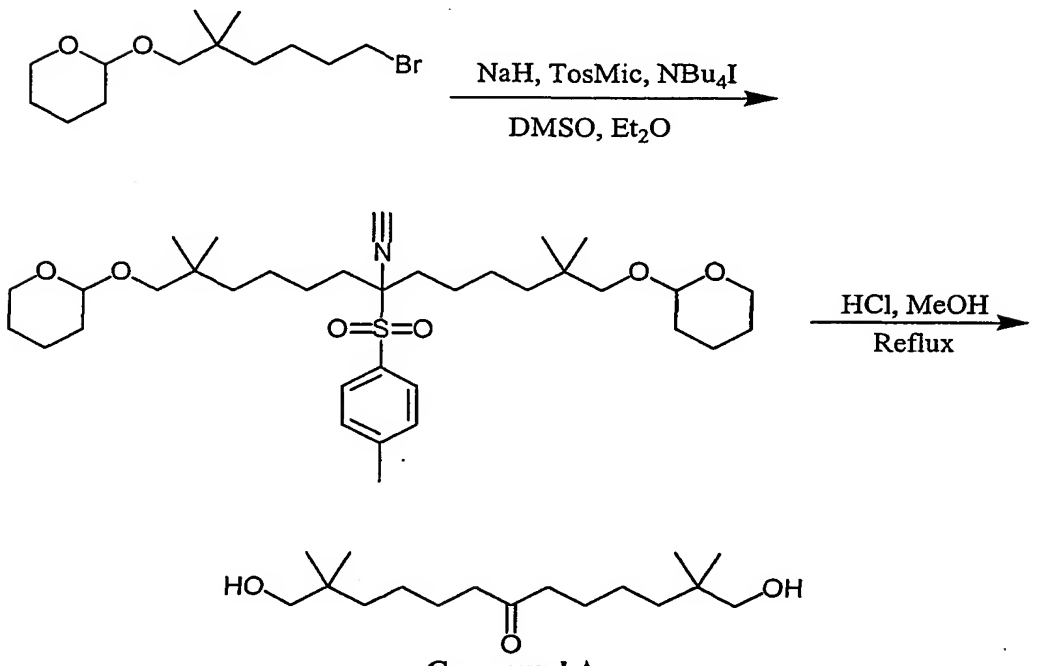
prevent or treat cardiovascular diseases include but are not limited to peripheral antiadrenergic drugs, centrally acting antihypertensive drugs (*e.g.*, methyldopa, methyldopa HCl), antihypertensive direct vasodilators (*e.g.*, diazoxide, hydralazine HCl), drugs affecting renin-angiotensin system, peripheral vasodilators, phentolamine, antianginal drugs, cardiac glycosides, inodilators (*e.g.*, amrinone, milrinone, enoximone, fenoximone, imazodan, sulmazole), antidysrhythmic drugs, calcium entry blockers, ranitine, bosentan, and rezulin.

4.9. Combination Therapy for Cancer Treatment

The present compositions can be administered together with treatment with irradiation or one or more chemotherapeutic agents. For irridiation treatment, the irradiation can be gamma rays or X-rays. For a general overview of radiation therapy, see Hellman, Chapter 12: Principles of Radiation Therapy Cancer, in: Principles and Practice of Oncology, DeVita *et al.*, eds., 2nd. Ed., J.B. Lippencott Company, Philadelphia. Useful chemotherapeutic agents include methotrexate, taxol, mercaptopurine, thioguanine, hydroxyurea, cytarabine, cyclophosphamide, ifosfamide, nitrosoureas, cisplatin, carboplatin, mitomycin, dacarbazine, procarbizine, etoposides, campathecins, bleomycin, doxorubicin, idarubicin, daunorubicin, dactinomycin, plicamycin, mitoxantrone, asparaginase, vinblastine, vincristine, vinorelbine, paclitaxel, and docetaxel. In a specific embodiment, a composition of the invention further comprises one or more chemotherapeutic agents and/or is administered concurrently with radiation therapy. In another specific embodiment, chemotherapy or radiation therapy is administered prior or subsequent to administration of a present composition, preferably at least an hour, five hours, 12 hours, a day, a week, a month, more preferably several months (*e.g.*, up to three months), subsequent to administration of a composition of the invention.

5. EXAMPLES

5.1.a. Synthesis of 1,13-Dihydroxy-2,2,12,12-tetramethyl-tridecan-7-one also known as Compound A



Compound A

1,13-Dihydroxy-2,2,12,12-tetramethyl-tridecan-7-one

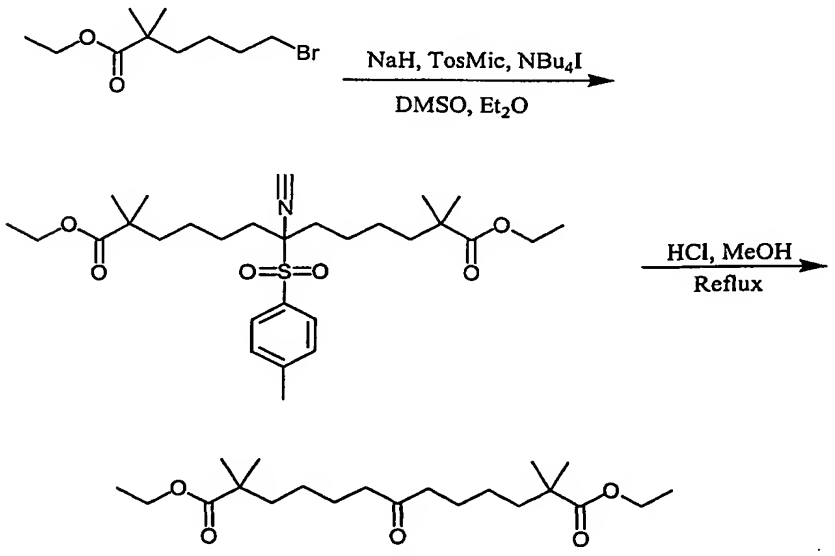
1,13-Dihydroxy-2,2,12,12-tetramethyl-tridecan-7-one

To a solution of 2-(6-bromo-2,2-dimethyl-hexyloxy)-tetrahydro-pyran (13.0 g, 44.33 mmol) and p-toluenesulphonylmethyl isocyanide (4.33 g, 22.17 mmol) in anhydrous DMSO (50 ml) and anhydrous diethyl ether (50 ml) was added sodium hydride (60% dispersion in mineral oil, 2.13 g, 53.20 mmol) at rt under N_2 atmosphere. After solidification of the

reaction mixture, additional anhydrous DMSO (50 ml) was added. After stirring for 5.5 h at room temperature, tetrabutylammonium iodide (1.64 g, 4.43 mmol) was added and the mixture stirred for additional 22.5 h at rt. The reaction mixture was carefully hydrolyzed with water (10 ml), diluted with water (200 ml), and extracted with diethyl ether (200 ml). The organic layer was washed with saturated NaCl solution (100 ml), dried over $MgSO_4$, and concentrated *in vacuo* to give crude 2-[7-isocyano-2,2,12,12-tetramethyl-13-(tetrahydro-pyran-2-yloxy)-7-(toluene-4-sulfonyl)- tridecyloxy]-tetrahydro-pyran (15.5 g) as an oil.

The crude material (14.8 g) was dissolved in methanol (180 ml), concentrated HCl (20 ml), and water (40 ml) and heated to reflux for 2 h. The reaction mixture was poured into CH_2Cl_2 (200 ml) and saturated NaCl solution (200 ml). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (200 ml). The combined organic layers were washed with saturated $NaHCO_3$ solution (2 x 100 ml) and brine (100 ml), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting crude oil was purified by flash chromatography (silica; hexanes/ethyl acetate = 1/1) to give the pure product (4.3 g, 71 % over two steps) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ = 3.28 (s, 4 H); 2.80 (m, 2 H); 2.42 (t, 4 H, J = 7.3); 1.54 (m, 4 H); 1.25 (m, 8 H); 0.84 (s, 12 H). ^{13}C NMR ($CDCl_3$, 75 MHz) 212.06, 71.24, 42.47, 38.11, 34.76, 24.45, 23.72, 23.25.

5.1.b. Synthesis of 2,2,12,12-Tetramethyl-7-oxo-tridecanedioic acid diethyl ester also referred to herein as Compound B diethyl ester



Compound B diethyl ester

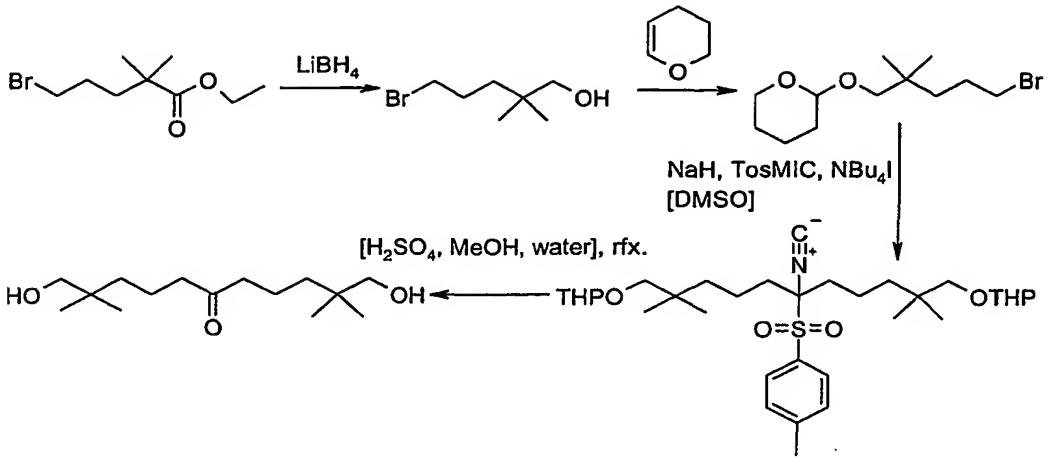
2,2,12,12-Tetramethyl-7-oxo-tridecanedioic acid diethyl ester

2,2,12,12-Tetramethyl-7-oxo-tridecanedioic acid diethyl ester

Under N_2 atmosphere, to a solution of ethyl-(5-bromo-2,2-dimethyl-pentanoate (11.1 g, 44.2 mol) in DMSO (150 ml, dried over 4 Å molecular sieves) was added *p*-toluenesulphonylmethyl isocyanide (4.31 g, 22.1 mmol), sodium hydride (60 % w/w in mineral oil, 2.12 g, 53.02 mmol), and tetra-n-butyl ammonium iodide at rt. The reaction mixture was stirred for 18 h at rt, then cooled to 0 °C, carefully hydrolyzed with water (10 ml), and then diluted with additional water (250 ml). The solution was extracted with diethyl ether (3 x 150 ml). The combined organic layers were washed with saturated NaCl solution (2 x 100 ml), dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and dried in high *vacuo* to give the p-toluenesulphonyl intermediate (11.1 g, 93 %) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.85 (d, 2 H, J = 8.3); 7.43 (d, 2 H, J = 8.3); 4.12 (q, 4 H, J = 7.0); 2.49 (s, 3 H); 1.94 (m, 4 H); 1.60 - 1.34 (m, 8 H); 1.30 - 1.15 (m, 4 H); 1.25 (t, 6 H, J = 7.0); 1.15 (s, 12 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 177.77, 164.08, 146.43, 131.20, 130.34, 129.96, 81.78, 60.37, 42.12, 40.27, 33.21, 25.25, 25.19, 24.97, 24.26, 21.86, 14.34.

To a solution intermediate (11.0 g, 20.53 mmol) in CH_2Cl_2 (250 ml) was added concentrated HCl (50 ml) and the reaction mixture was stirred for 30 min at rt. The solution was diluted with water (200 ml) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (200 ml). The combined organic layers were washed with saturated $NaHCO_3$ solution (2 x 100 ml), half-saturated NaCl solution (100 ml), and saturated NaCl solution. The organic phases were dried over $MgSO_4$, concentrated *in vacuo*, and dried in high *vacuo* to furnish crude compound B ethyl ester (8.2 g, 108 %) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.03 (q, 4 H, J = 7.1); 2.31 (t, 4 H, J = 7.5); 1.45 (m, 8 H); 1.20 - 1.08 (m, 4 H); 1.16 (t, 6 H, J = 7.1); 1.07 (s, 12 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 211.14, 178.05, 60.34, 42.69, 42.20, 40.52, 25.24, 24.71, 24.30, 14.35.

5.1.c. Synthesis of 1,11-Dihydroxy-2,2,10,10-tetramethyl-undecan-6-one



5-Bromo-2,2-dimethyl-pentan-1-ol

In a 1-L 3-neck round-bottomed flask fitted with condenser, dropping funnel pressure equalizer and magnetic stirrer were placed dichloromethane (300 mL) and lithium borohydride (12.97 g, 0.595 moles). The mixture was heated to 28-30 °C, then the heating was discontinued and methanol (19.04 g, 0.595 moles) was added, at a rate that maintained the temperature below 30 °C. To this solution, ethyl 5-bromo-2,2-dimethylpentanoate (94 g, 0.397 mol) in dichloromethane (100 mL) was added under argon atmosphere, allowing a gentle reflux during the addition. After the completion of the addition, the mixture was heated to 36-40 °C until no more starting material was detected by GC. The reaction mixture was cooled to 0 °C and was treated with crushed ice (130 g) under vigorous stirring until the effervescence ceased. The reaction mixture was treated with saturated aqueous NH_4Cl (120 mL), stirred for 25 min, and warmed to above 15 °C. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic phases were washed with saturated aqueous NH_4Cl (2 × 100 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give 5-bromo-2,2-dimethyl-pentan-1-ol (78 g, 88.1 % yield). ^1H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 5.02 (s, 1 H), 3.39-3.34 (t, J = 14, 2 H), 3.33 (s, 2 H), 1.85-1.75 (m, 2 H), 1.38-1.31(m, 2 H), 0.88 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$ = 77.0 ppm /TMS): δ (ppm) 71.5, 37.1, 34.8, 34.6, 27.6, 23.8.

5-Bromo-1-(tetrahydropyranyloxy)-2,2-dimethylpentane

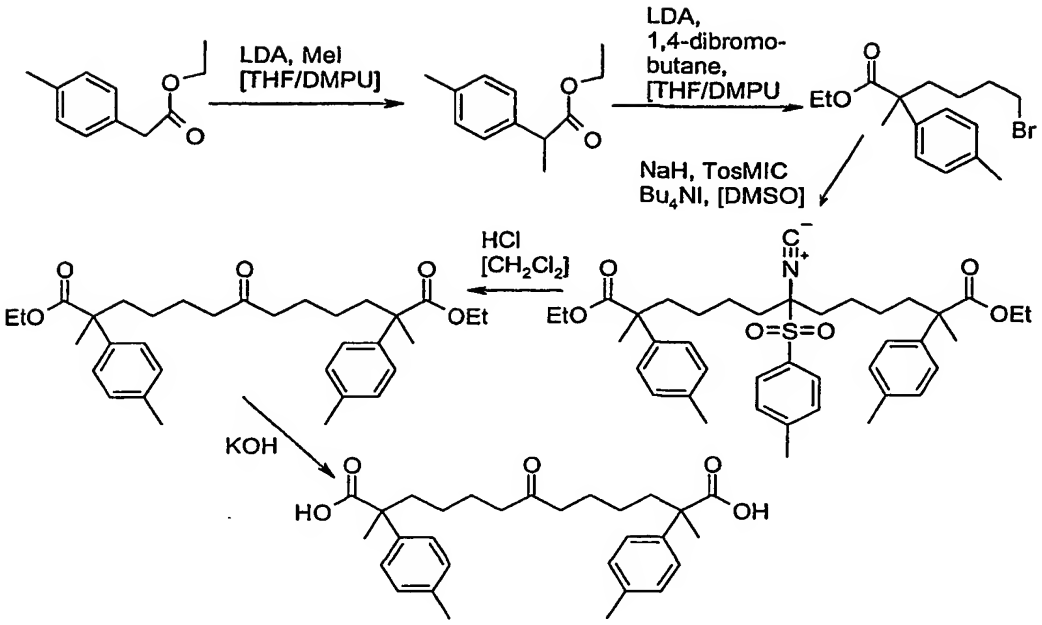
To a solution of 5-bromo-2,2-dimethyl-1-pentanol (78 g, 0.35 mol) and *p*-toluenesulfonic acid (0.42 g) in dichloromethane (0.5 L) was added 3,4-dihydro-2H-pyran (45 mL) slowly at 0 °C. The reaction mixture was stirred at rt overnight, or until no more starting material was evidenced by TLC. The mixture was filtered through aluminum oxide and was washed with dichloromethane (300 mL). The filtrate was evaporated under vacuum to produce 5-bromo-1-(tetrahydropyranyloxy)-2,2-dimethylpentane (101 g, 94.7 % yield) as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 4.48 - 4.52 (m, 1 H), 3.90 - 3.75 (m, 1 H), 3.50 - 3.35 (m, 4 H), 2.95 (d, J = 12 Hz, 1 H), 1.90 - 1.20 (m, 10 H), 0.90 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$ = 77.0 ppm/TMS): δ (ppm) 99.2, 76.3, 62.0, 38.0, 34.9, 34.2, 30.7, 28.0, 25.7, 24.8, 24.7, 19.3.

1,11-Dihydroxy-2,2,10,10-tetramethyl-undecan-6-one

Under N_2 atmosphere, to a solution of 5-bromo-1-(tetrahydropyranyloxy)-2,2-dimethylpentane (40.0 g, 0.143 mol) and *p*-toluenesulphonylmethyl isocyanide (TosMIC; 13.99 g, 0.072 mol) in anhydrous DMSO (400 mL) was added sodium hydride (60% dispersion in mineral oil, 6.86 g, 0.173 mol) under cooling in a water-bath. Tetra-*n*-butylammonium iodide (5.28 g, 0.0143 mol) was then added while cooling in a water-bath. The mixture was stirred for 6 h at rt., then carefully hydrolyzed by drop-wise addition of water (100 mL) under cooling in a water-bath. The reaction mixture was diluted with dichloromethane (100 mL), additional water (100 mL), and dichloromethane (100 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with water (2 × 200 mL) and saturated NaCl solution (100 mL), dried over $MgSO_4$, concentrated *in vacuo*, and dried in high *vacuo* to give crude 2-[6-isocyano-2,2,10,10-tetramethyl-11-(tetrahydropyran-2-yloxy)-6-(toluene-4-sulfonyl)-undecyloxy]-tetrahydropyran (47.9 g) as a brownish, viscous oil. This crude oil (47.0 g) was dissolved in methanol (200 mL) and water (40 mL). Concentrated sulfuric acid (20 mL) was added drop-wise over 10 min whereupon the solution warmed up to ca. 30 °C. The reaction mixture was stirred at rt for ca. 150 min and then diluted with water (200 mL). The mixture was extracted with CH_2Cl_2 (2 × 200 mL, 1 x 100 mL) and the combined organic layers were washed with water (200 mL), 10 % potassium hydroxide solution (3 × 200 mL), water (200 mL), and brine (160 mL). The organic extracts were dried over $MgSO_4$, concentrated *in vacuo*, and dried in high *vacuo* to furnish crude 1,11-dihydroxy-2,2,10,10-tetramethyl-undecan-6-one (26.0 g) as a brown oil. The crude product was purified by chromatography (silica, 330 g, hexanes/ethyl acetate = 90/10, 70/30, 50/50) to

obtain three fractions: A: 1.1 g, 93.5 % purity by HPLC, 5.6 % yield; B: 3.0 g, ca. 96.7 % purity by HPLC, 16 % yield, and C: 4.0 g, ≥ 90 % purity by NMR, 19.5 %. Fraction C was again purified by chromatography (silica, 150 g, hexanes/ethyl acetate = 60/40) to give clean product (1.5 g, purity by HPLC: 96.3 %). Overall yield: 5.6 g, 30.3 % over two steps. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 3.25 (s, 4 H), 2.60 (br., 2 H), 2.32 (t, 4 H, J = 7.2), 1.45 (m, 4 H), 1.12 (m, 4 H), 0.79 (s, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$ = 77.0 ppm/TMS): δ (ppm) 212.25, 70.99, 43.15, 37.69, 34.94, 23.89, 17.91. HRMS (LSIMS, gly): Calcd for $C_{15}H_{29}O_2$ ($MH^+ - H_2O$): 241.2168, found: 241.2169.

5.1.d. Synthesis of 2,12-Dimethyl-7-oxo-2,12-di-*p*-tolyl-tridecanedioic acid



2-*p*-Tolyl-propionic acid ethyl ester

Under N_2 atmosphere, a solution of ethyl *p*-tolyl-acetate (2.72 g, 15.2 mmol) in anhydrous THF (70 mL) was cooled to - 40 °C and a solution of LDA (7.6 mL, 15.25 mmol) was added drop-wise over 30 minutes. The reaction mixture was stirred for 1 h, and methyl iodide (3.03 g, 21.30 mmol) was added drop-wise, followed by the addition of DMPU (1 mL). The reaction mixture was allowed to warm to rt, after 1 h and stirred overnight. The reaction mixture was poured into water (30 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated NH_4Cl solution (10 mL), 1 M HCl (10 mL), saturated $NaHCO_3$ solution (10 mL), and brine (10 mL), then dried over $MgSO_4$, and concentrated *in vacuo*. The residue was distilled in high *vacuo* (bp. 59 - 63 °C/0.2 mmHg) to furnish 2-*p*-tolyl-propionic acid ethyl ester (2.5 g, 86.0%) as an oil. ^1H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 7.18 (d, 2 H, J = 8.1), 7.10 (d, 2 H, J = 8.1), 4.09 (m, 2 H), 3.67 (q, 1 H, J = 7.2), 2.29 (s, 3 H), 1.47 (d, J = 7.2 Hz, 3 H), 1.20 (t, J = 5.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 174.71, 137.80, 136.63, 129.33, 129.14, 127.36, 60.66, 45.18, 21.05, 18.70, 14.15. [Lit. ref.: Ghosh, S.; Pardo, S. N.; Salomon, R. G. *J. Org. Chem.* **1982**, *47*, 4692 - 4702.].

6-Bromo-2-methyl-2-*p*-tolyl-hexanoic acid ethyl ester

Under N_2 atmosphere, LDA (54.5 mL, 110 mmol) was added drop-wise to a stirred solution of 2-*p*-tolyl-propionic acid ethyl ester (21 g, 110 mmol) in anhydrous THF (190 mL) at - 78 °C. After 1 h, the reaction mixture was added to a solution of 1,4-dibromo-butane (38 g, 176 mmol) in THF (50 mL) at -78 °C, followed by addition of DMPU (20 mL). The reaction mixture was stirred for 2 h, then warmed to rt overnight. The resulting mixture was poured into saturated NH_4Cl solution (1000 mL), and extracted with ethyl acetate (4 × 250 mL). The combined organic layers were washed with brine (300 mL), 1 M HCl (200 mL), saturated $NaHCO_3$ solution (300 mL), and brine (200 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled in high *vacuo* (bp. 128 - 130 °C/0.2 mmHg) to furnish 6-bromo-2-methyl-2-*p*-tolyl-hexanoic acid ethyl ester (22 g, 89.5 %) as an oil. ^1H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 7.19 (d, 2 H, J = 8.2 Hz), 7.12 (d, 2 H, J = 8.2 Hz), 4.13 (q, 2 H, J = 7.2 Hz), 3.37 (t, J = 6.6 Hz, 2 H), 2.32 (s, 3 H), 2.10 - 1.80 (m, 4 H), 1.54 (s, 3 H), 1.36 (m, 2 H), 1.19 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 176.26, 140.92, 136.35, 129.21, 125.89, 60.88, 49.82, 38.53, 33.61, 33.33, 23.59, 22.78, 21.07, 14.25. HRMS (LSIMS, nba): Calcd. for ($C_{16}H_{23}BrO_2$) 327.0959, found 327.0975.

2,12-Dimethyl-7-oxo-2,12-di-*p*-tolyl-tridecanedioic acid diethyl ester

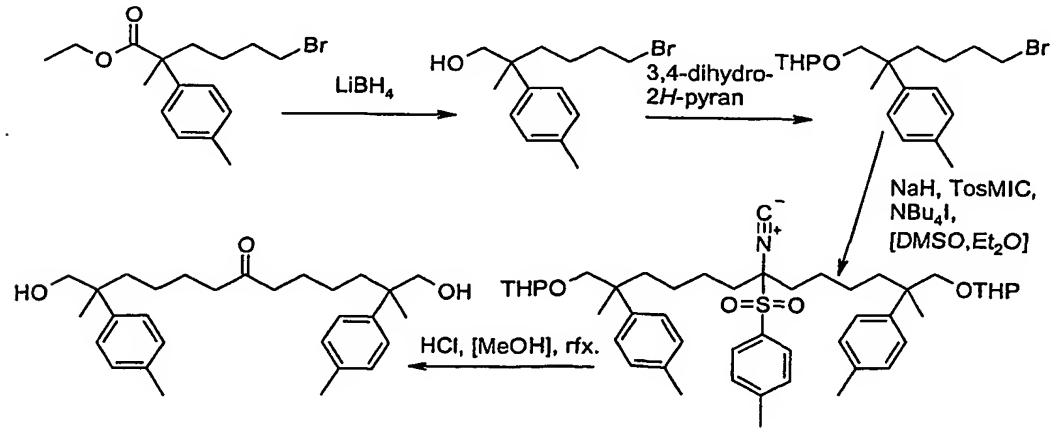
To a solution of 6-bromo-2-methyl-2-*p*-tolyl-hexanoic acid ethyl ester (21 g, 64.22 mmol), tetra-*n*-butylammonium iodide (2.37 g, 6.42 mmol), and *p*-toluene-sulphonylmethyl isocyanide (TosMIC, 6.26g, 32.11 mmol) in anhydrous DMSO (320 mL) and anhydrous diethyl ether (110 mL) was added sodium hydride (60% dispersion in mineral oil, 3.24 g, 80.92 mmol) at rt under N_2 atmosphere. The reaction mixture was stirred for 24 h at rt, then carefully hydrolized with ice-water (600 mL) and extracted with diethyl ether (2 × 300 mL). The combined organic layers were washed with brine (2 × 300 mL), dried over $MgSO_4$, and concentrated to furnish a crude 2,12-dimethyl-7-isocyano-2,12-di-*p*-tolyl-7-(toluene-4-sulfonyl)-tridecanedioic acid diethyl ester. A solution of this crude intermediate in CH_2Cl_2 (500 mL) and concd HCl (140 mL) was stirred for 2 h at rt. The reaction mixture was diluted with water (500 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (150 mL), and brine (150 mL), dried over $MgSO_4$, and concentrated in vacuo. The resulting crude oil was purified by flash chromatography (silica gel, ethyl acetate/hexanes = 1/20, 1/10) to furnish 2,12-dimethyl-7-oxo-2,12-di-*p*-tolyl-tridecanedioic acid diethyl ester (9.0 g, 67.12%) as a light yellowish oil. ^1H NMR (300 MHz,

$CDCl_3$/TMS): δ (ppm) 7.10 (d, 4 H, J = 7.9 Hz), 7.02 (d, 4 H, J = 7.9 Hz), 4.05 (q, 4 H, J = 7.0 Hz), 2.25 (t, J = 9 Hz, 4 H), 2.20 (s, 6 H), 1.95 - 1.70 (m, 4 H), 1.42 (s, 6 H), 1.50 - 1.05 (m, 8 H), 1.08 (t, 6 H, J = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 211.10, 176.00, 141.00, 135.80, 128.50, 124.51, 60.50, 49.50, 42.01, 39.50, 24.05, 22.10, 20.50, 13.00. HRMS (LSIMS, nba): Calcd. for $C_{33}H_{47}O_5$ (MH^+): 523.3424 , found: 523.3405.

2,12-Dimethyl-7-oxo-2,12-di-*p*-tolyl-tridecanedioic acid

2,12-Dimethyl-7-oxo-2,12-di-*p*-tolyl-tridecanedioic acid diethyl ester (9.0 g, 17.24 mmol) was added to a homogenous solution of KOH (85%, 4.0 g, 60.34 mmol) in water (10 mL) and ethanol (30 mL). The reaction mixture was heated to reflux for 6 h. The ethanol was removed under reduced pressure. The residue was diluted with water (30 mL) and the solution was acidified with concd. HCl (12 mL) to pH 1, then extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by flash chromatography (silica gel, ethyl acetate/hexanes = 1/20, 1/10, 1/2) to furnish 2,12-dimethyl-7-oxo-2,12-di-*p*-tolyl-tridecanedioic acid (3.1 g, 38.8%) as a white solid. Mp.: 48 - 50 °C. ^1H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 9.69 (br, 2 H), 7.22 (d, 4 H, J = 8.1), 7.12 (d, 4 H, J = 8.1), 2.36 (t, J = 7.5 Hz, 4 H), 2.31 (s, 6 H), 1.98 - 1.80 (m, 4 H), 1.56 - 1.44 (m, 4 H), 1.51 (s, 6 H), 1.24 - 1.15 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 211.63, 183.07, 140.40, 137.00, 129.58, 126.43, 50.02, 42.82, 39.10, 24.74, 24.50, 22.82, 21.39. HRMS (LSIMS, nba): Calcd. for $C_{29}H_{39}O_5$ (MH^+): 467.2797, found: 467.2785.

5.1.e. Synthesis of 1,13-Dihydroxy-2,12-dimethyl-2,12-di-*p*-tolyl-tridecan-7-one



6-Bromo-2-methyl-2-*p*-tolyl-hexan-1-ol

Methanol (3.14 g, 98.22 mmol) was added drop-wise to a stirred suspension of $LiBH_4$ (2.19 g, 101 mmol) in anhydrous CH_2Cl_2 (50 mL) under N_2 atmosphere. After the addition of ethyl 6-bromo-2-methyl-2-*p*-tolyl-hexanoate (22 g, 67.28 mmol), the reaction mixture was heated to reflux overnight. The reaction mixture was cooled to 5 °C and hydrolized with ice (ca. 40 g) and saturated NH_4Cl solution (150 mL) for 1 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with saturated NH_4Cl solution (3 × 150 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo to furnish 6-bromo-2-methyl-2-*p*-tolyl-hexan-1-ol (18.44 g, 96.2 %) as an oil. ^1H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 7.25 - 7.00 (m, 4 H), 3.68 - 3.50 (m, 1 H), 3.49 - 3.35 (m, 1 H), 3.34 - 3.21 (t, J = 6.9 Hz, 2 H), 2.31 (s, 3 H), 1.88 - 1.51 (m, 4 H), 1.51 - 1.40 (m, 2 H), 1.31 (s, 3 H), 1.20 - 1.00 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 141.49, 135.74, 129.47, 126.63, 72.54, 43.03, 37.53, 33.69, 33.51, 22.66, 21.58, 20.98. HRMS (LSIMS, nba): Calcd. for $C_{14}H_{20}Br$ ($MH^+ - H_2O$): 267.0748 , found: 267.0750.

2-(6-Bromo-2-methyl-2-*p*-tolyl-hexyloxy)-tetrahydropyran

Under N_2 atmosphere, 3,4-dihydro-2*H*-pyran (6.39 g, 76.09 mmol) was added drop-wise to a stirred solution of 6-bromo-2-methyl-2-*p*-tolyl-hexan-1-ol (18.20 g, 63.86 mmol) and *p*-toluenesulfonic acid hydrate (0.43 g, 2.26 mmol) in dichloromethane (300 mL) at - 5 °C. The reaction mixture was allowed to warm to rt and stirred for 3 h. The solution was filtered through aluminum oxide (160 g), which was washed with CH_2Cl_2 (500 mL). The filtrate was concentrated *in vacuo* to furnish 2-(6-bromo-2-methyl-2-*p*-tolyl-hexyloxy)-tetrahydropyran (22 g, 93.4 %) as an oil. ^1H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 7.25 - 7.05 (m, 4 H), 4.60 - 4.48 (m, 1 H), 3.82 (m, 2 H), 3.48 - 3.37 (m, 2 H), 3.35 - 3.26 (m, 2 H), 2.30 (s, 3 H), 1.90 - 1.40 (m, 11 H), 1.40 - 1.33 (s, 3 H), 1.40 - 1.08 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 142.78, 135.22, 128.81, 126.39, 99.09, 61.99, 41.67, 38.12, 37.87, 33.68, 30.99, 25.96, 23.08, 22.89, 21.12, 20.97, 19.41. HRMS (LSIMS, nba): Calcd. for $C_{19}H_{30}O_2Br$ (MH+): 369.1429 , found: 369.1451.

1,13-Dihydroxy-2,12-dimethyl-2,12-di-*p*-tolyl-tridecan-7-one

To a solution of 2-(6-bromo-2-methyl-2-*p*-tolyl-hexyloxy)-tetrahydropyran (21.5 g, 58.27 mmol), tetra-*n*-butylammonium iodide (2.36 g, 6.41 mmol), and *p*-toluenesulphonyl-methyl isocyanide (TosMIC, 5.68 g, 29.14 mmol) in anhydrous DMSO (300 mL) and anhydrous diethyl ether (100 mL) was added sodium hydride (60% dispersion in mineral oil, 2.94 g, 73.42 mmol) at rt under N_2 atmosphere. The mixture was stirred for 24 h at rt. The reaction mixture was carefully hydrolized with ice-water (500 mL) and extracted with diethyl ether (2 × 300 mL). The organic layer was washed with brine (2 × 300 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to furnish crude 2-[7-isocyano-2,12-dimethyl-2,12-di-*p*-tolyl-13-(tetrahydropyran-2-yloxy)-7-(toluene-4-sulfonyl)-tridecanyloxy]-tetrahydropyran (18.44 g) as a brown oil. A solution of this crude intermediate (18 g) in methanol (300 mL), concd. HCl (36 mL), and water (70 mL) was heated to reflux for 3 h. The reaction mixture was poured into CH_2Cl_2 (250 mL) and ice-water (250 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (3 × 100 mL) and brine (150 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting crude oil was purified by flash chromatography (silica gel, ethyl acetate/hexanes = 20/1, 15/1, 10/1, 5/1, and 1/1) to furnish 1,13-dihydroxy-2,12-dimethyl-2,12-di-*p*-tolyl-tridecan-7-one (2.72 g, 26.2 % over two steps) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 7.18 (d, 4 H, J = 8.1 Hz), 7.12 (d, 4 H, J = 8.1 Hz), 3.63 (d, J = 11.0 Hz, 2 H), 3.49 (d, J = 11.0 Hz, 2 H), 2.31 (s, 6 H), 2.26 (t, J = 7.8 Hz, 4 H), 1.78-1.40 (m, 10 H), 1.28 (s, 6 H), 1.24 - 0.82 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 211.51, 141.75, 135.64, 129.23, 126.64, 72.54, 43.06, 42.65, 38.28, 24.53, 23.59, 21.66, 20.98. HRMS (LSIMS, nba): Calcd. for $C_{29}H_{43}O_3$ (MH^+): 439.3212, found: 439.3222.

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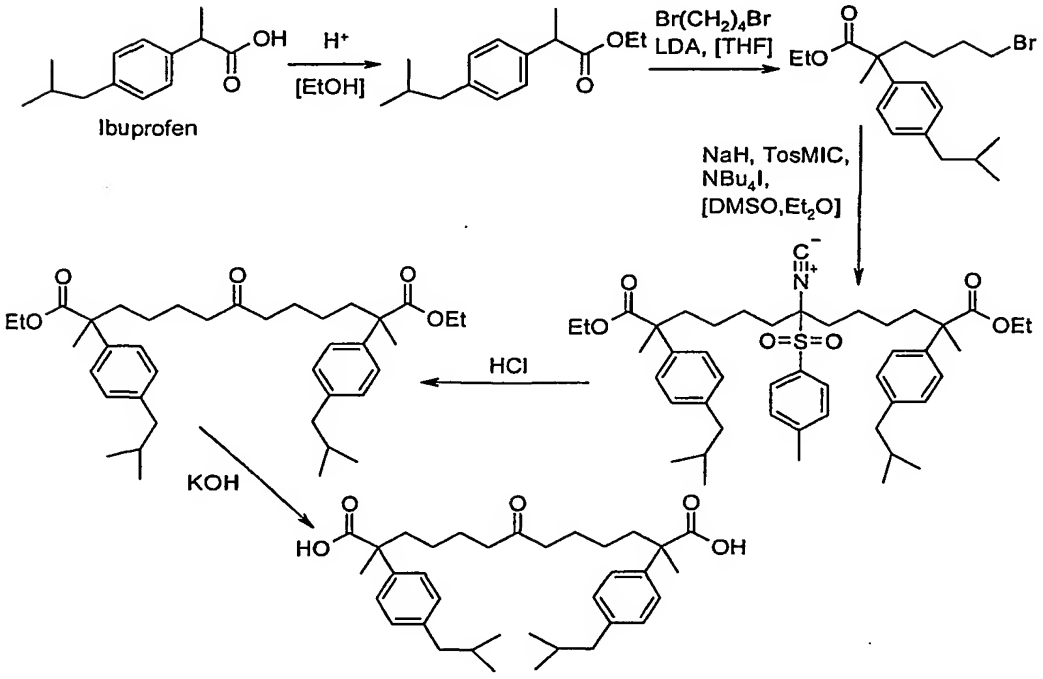
5.1.f. Synthesis of 2,12-*Bis*-(4-isobutyl-phenyl)-2,12-dimethyl-7-oxo-tridecanedioic acid



10

6-Bromo-2-(4-isobutyl-phenyl)-2-methyl-hexanoic acid ethyl ester

Ethyl (4-isobutyl-phenyl)-acetate (10.5 g, 44.8 mmol) was dissolved in freshly distilled tetrahydrofuran (150 mL) and cooled to -78 °C. Lithium diisopropylamide (2 N, 28 mL, 56 mmol) was added and the solution stirred for 1 hour at -78 °C under a nitrogen
15 atmosphere. 1,4-Dibromobutane (25 mL, 37.5 g, 175 mmol) was then added drop-wise over 30 minutes. The solution was allowed to warm to room temperature over five hours. After stirring at room temperature for an additional 16 hours, the reaction was quenched with water (100 mL) and extracted with diethyl ether (2 × 100 mL). The ether was washed with 10% hydrochloric acid (2 × 100 mL), saturated sodium bicarbonate (100 mL) and water

(100 mL). After drying with sodium sulfate (5 g), filtration and concentration, the product was purified by flash chromatography on silica gel (200 g), eluting with 5% ethyl acetate/hexanes. The product was then heated to 150 °C under vacuum (0.5 mm Hg) for 30 minutes to remove excess 1,4-dibromobutane. The reaction yielded 6-bromo-2-(4-isobutyl-phenyl)-2-methyl-hexanoic acid ethyl ester (14.49 g, 87.5% yield) as a clear, viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm): 7.19 (d, 2H, *J*= 8.0 Hz), 7.08 (d, 2H, *J*= 8.0 Hz), 4.11 (q, 2H, *J*= 7.0 Hz), 3.35 (t, 2H, *J*= 6.8 Hz), 2.43 (d, 2H, *J*= 7.3 Hz), 2.10 - 1.92 (m, 1H), 1.92 - 1.78 (m, 4H), 1.53 (s, 3H), 1.40 - 1.28 (m, 2H), 1.17 (t, 3H, *J*= 7.0 Hz), 0.88 (d, 6H, *J*= 6.8). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 176.17, 141.12, 140.04, 129.14, 125.64, 60.77, 49.80, 44.99, 38.52, 33.51, 33.26, 30.22, 23.55, 22.69, 22.50, 14.19. HRMS (LSIMS, nba): Calcd. for $C_{19}H_{30}O_2Br$ (MH^+): 369.1429, found: 369.1445.

2,12-*Bis*-(4-isobutyl-phenyl)-2,12-dimethyl-7-oxo-tridecanedioic acid diethyl ester

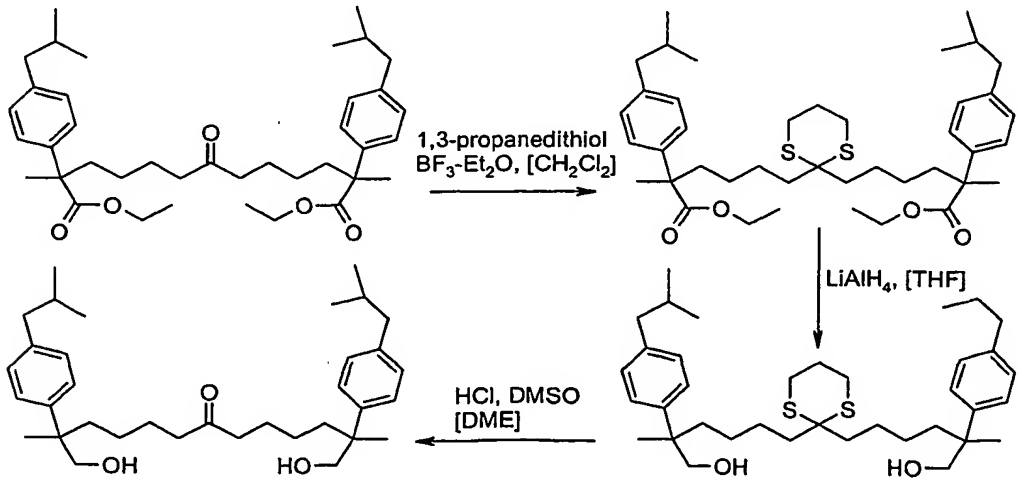
6-Bromo-2-(4-isobutyl-phenyl)-2-methyl-hexanoic acid ethyl ester (14.13 g, 38.2 mmol) was dissolved in freshly distilled methylsulfoxide (200 mL) and TosMIC (3.73 g, 19.1 mmol), tetra-*n*-butylammonium iodide (1.30 g, 3.5 mmol), and sodium hydride (2.0 g 60%, 19.1 mmol) were added at room temperature under a nitrogen atmosphere. After stirring for 18 hours at room temperature, the reaction was quenched by the slow addition of water (200 mL). Dichloromethane (100 mL) was added and the layers were separated. The aqueous fraction was then extracted with additional dichloromethane (2 × 50 mL). The dichloromethane fractions were combined and washed with water (100 mL) and brine (100 mL) before drying with sodium sulfate. After filtration, concentration and drying under high vacuum, the crude intermediate was dissolved in dichloromethane (100 mL) and concentrated hydrochloric acid (50 mL). After stirring for one hour at room temperature, cold water (200 mL) was added and the layers were separated. The aqueous portion was extracted with additional dichloromethane (100 mL). The dichloromethane fractions were combined, dried with sodium sulfate, filtered and concentrated. The product was purified by flash chromatography on silica gel (300 g), eluting with 10% ethyl acetate/hexanes (2 L) followed by 20 % ethyl acetate/hexanes (1 L). The reaction yielded 2,12-*bis*-(4-isobutyl-phenyl)-2,12-dimethyl-7-oxo-tridecanedioic acid diethyl ester (9.49 g, 82% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 7.18 (d, 4H, *J*= 8.0 Hz), 7.07 (d, 4H, *J*= 8.0 Hz), 4.10 (q, 4H, *J*= 7.0 Hz), 2.43 (d, 4H, *J*= 7.0 Hz), 2.34 (t, 4H, *J*= 7.6 Hz), 2.10-1.92 (m, 2H), 1.92-1.78 (m, 4H), 1.60-1.50 (m, 4H), 1.50 (s, 6H), 1.19-1.11 (m, 5H), 1.17 (t, 3H, *J*= 7.0 Hz), 0.88 (d, 12H, *J*= 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 211.06, 176.39, 141.36, 140.04, 129.16, 125.71, 60.77, 49.90, 45.06, 42.66, 39.18,

30.27, 24.59, 24.35, 22.86, 22.56, 14.23. HRMS (LSIMS, nba): Calcd. for $C_{39}H_{59}O_5$ (MH^+): 607.4362, found: 607.4337.

2,12-*Bis*-(4-isobutyl-phenyl)-2,12-dimethyl-7-oxo-tridecanedioic acid

2,12-*Bis*-(4-isobutyl-phenyl)-2,12-dimethyl-7-oxo-tridecanedioic acid diethyl ester (3.0 g, 4.95 mmol) was dissolved in ethanol (40 mL) and water (10 mL) with potassium hydroxide (4.4 g 85%). The solution was heated to reflux for six hours, cooled and concentrated. After the ethanol was removed, water (200 mL) was added and the solution was extracted with diethyl ether (100 mL). The aqueous fraction was acidified with concentrated hydrochloric acid (10 mL, to pH = 1). The product was then extracted with diethyl ether (2 × 100 mL). The ether fractions were combined and dried with sodium sulfate (5 g). After filtration, concentration and drying under high vacuum, the reaction yielded 2,12-*bis*-(4-isobutyl-phenyl)-2,12-dimethyl-7-oxo-tridecanedioic acid (2.35 g, 82% yield) as a light yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 10.02 (bs, 2H), 7.24 (d, 4H, *J*= 8.0 Hz), 7.09 (d, 4H, *J*= 8.0 Hz), 2.43 (d, 4H, *J*= 7.0 Hz), 2.33 (t, 4H, *J*= 7.3 Hz), 2.05-1.88 (m, 2H), 1.96-1.77 (m, 4H), 1.55-1.42 (m, 10H), 1.22-1.08 (m, 4H), 0.88 (d, 12H, *J*= 6.6). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm): 211.48, 182.94, 140.43, 140.24, 129.27, 125.94, 49.71, 45.06, 42.58, 42.58, 38.91, 30.25, 24.45, 24.24, 22.58, 22.40. HRMS (LSIMS, nba): Calcd. for $C_{35}H_{50}O_5Na$ (MNa^+): 573.3555, found: 573.3459.

5.1.g. Synthesis of 1,13-Dihydroxy-2,12-*bis*-(4-isobutyl-phenyl)-2,12-dimethyl-tridecan-7-one



2,12-*Bis*-(4-isobutyl-phenyl)-2,12-dimethyl-7-([1,3]dithianyl)-tridecanedioic acid diethyl ester

2,12-*Bis*-(4-isobutyl-phenyl)-2,12-dimethyl-7-oxo-tridecanedioic acid diethyl ester (5.50 g, 9.0 mmol) was dissolved in freshly distilled dichloromethane (60 mL) with borontrifluoride etherate (0.45 mL) and 1,3-propanedithiol (1.0 mL, 0.98 g, 9.0 mmol). The solution was stirred for three hours at room temperature under a nitrogen atmosphere. After three hours, an additional volume of dichloromethane (100 mL) was added and the solution was extracted with 5% sodium hydroxide solution (2 × 50 mL) and water (100 mL). After drying with sodium sulfate, filtration, and concentration, the product was purified by flash chromatography on silica gel (130 g), eluting with 10% ethyl acetate/hexanes. The reaction yielded 2,12-*bis*-(4-isobutyl-phenyl)-2,12-dimethyl-7-([1,3]dithianyl)-tridecanedioic acid diethyl ester (6.16 g, 98% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 7.20 (d, 4H, *J*= 8.0 Hz), 7.07 (d, 4H, *J*= 8.0 Hz), 4.10 (q, 4H, *J*= 7.0 Hz), 2.76 (t, 4H, *J*= 5.3 Hz), 2.43 (d, 4H, *J*= 7.0 Hz), 2.09-1.95 (m, 2H), 1.94-1.78 (m, 10H), 1.51 (s, 6H), 1.46-1.36 (m, 4H), 1.25-1.12 (m, 4 H), 1.18 (t, 6 H, *J* = 7.0 Hz), 0.88 (d, 12H, *J*= 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 176.42, 141.43, 140.00, 129.14, 125.74, 60.74, 53.30, 49.97, 45.05, 39.22, 38.29, 30.26, 26.10, 25.64, 25.17, 24.76, 22.99, 22.56, 14.26. HRMS (LSIMS, nba): Calcd. for $C_{42}H_{65}O_4S_2$ (MH^+): 696.4246, found: 696.4234.

2,12-*Bis*-(4-isobutyl-phenyl)-2,12-dimethyl-7-([1,3]dithianyl)-tridecane-1,13-diol

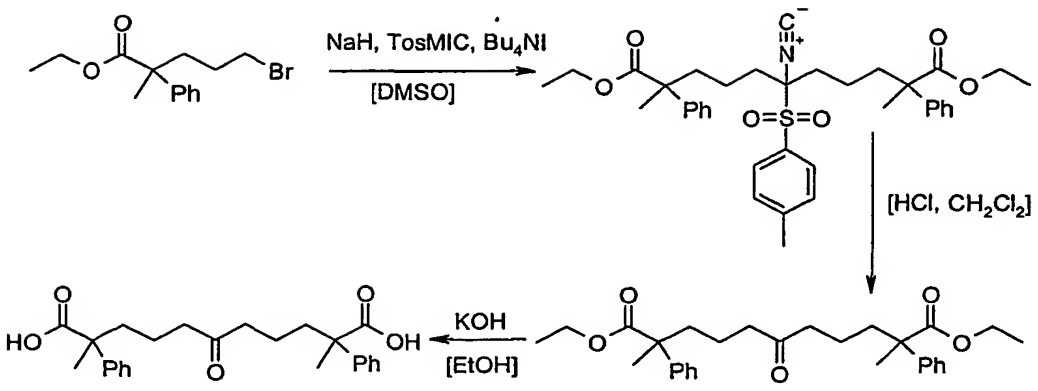
2,12-*Bis*-(4-isobutyl-phenyl)-2,12-dimethyl-7-([1,3]dithianyl)-tridecanedioic acid diethyl ester (5.81 g, 8.33 mmol) was dissolved in freshly distilled tetrahydrofuran (THF, 50 mL) and added to lithium aluminum hydride (1.0 g, 26.3 mmol) in THF (50 mL) at -78 °C under a nitrogen atmosphere. The solution was warmed to room temperature over four hours. The reaction was then cooled back to -78 °C and quenched with ethyl acetate (5.0 mL). After warming to room temperature, water (100 mL) was added and the product was extracted with diethyl ether (2 × 100 mL). The ether extracts were combined, dried with sodium sulfate, filtered, and concentrated. After drying under high vacuum for four hours, the reaction yielded 2,12-*bis*-(4-isobutyl-phenyl)-2,12-dimethyl-7-([1,3]dithianyl)-tridecane-1,13-diol (4.80 g, 94% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 7.20 (d, 4H, *J*= 8.0 Hz), 7.09 (d, 4H, *J*= 8.0 Hz), 3.64 (d, 2H, *J*= 10.7 Hz), 3.48 (d, 2H, *J*= 10.7 Hz), 2.71 (t, 4H, *J*= 5.1 Hz), 2.50 - 2.35 (m br., 2 H), 2.43 (d, 4H, *J*= 7.0 Hz), 1.90-1.80

(m, 4H), 1.80-1.68 (m, 6H), 1.58-1.42 (m, 2H), 1.38-1.25 (m, 4H), 1.30 (s, 6H), 1.26-1.10 (m, 2H), 1.10-0.95 (m, 2H), 0.89 (d, 12H, *J*= 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 141.94, 139.39, 129.20, 126.44, 72.48, 53.30, 44.97, 43.09, 38.45, 38.18, 30.21, 26.01, 25.64, 24.84, 24.09, 22.55, 21.64. HRMS (LSIMS, nba): Calcd. for $C_{38}H_{61}O_2S_2$ (MH^+): 613.4113, found: 613.4075.

1,13-Dihydroxy-2,12-*bis*-(4-isobutyl-phenyl)-2,12-dimethyl-tridecan-7-one

2,12-*Bis*-(4-isobutyl-phenyl)-2,12-dimethyl-7-([1,3]dithianyl)-tridecane-1,13-diol (4.50 g, 7.35 mmol) was dissolved in dimethoxyethane (DME, 50 mL) with concentrated hydrochloric acid (10 mL). Methylsulfoxide (DMSO, 5.0 mL) was added drop-wise over five minutes and the solution was stirred for thirty minutes at room temperature. The reaction was then slowly poured into saturated sodium bicarbonate solution (100 mL) and extracted with diethyl ether (2 × 100 mL). The ether fractions were combined, dried with sodium sulfate, filtered, and concentrated. The product was purified by flash chromatography on silica gel (100 g), eluting with 30 % ethyl acetate/hexanes. The reaction yielded 1,13-dihydroxy-2,12-*bis*-(4-isobutyl-phenyl)-2,12-dimethyl-tridecan-7-one (3.2 g, 83.5 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm): 7.19 (d, 4H, *J*= 8.0 Hz), 7.09 (d, 4H, *J*= 8.0 Hz), 3.63 (d, 2H, *J*= 11.0 Hz), 3.49 (d, 2H, *J* = 11.0 Hz), 2.43 (d, 4H, *J*= 7.0 Hz), 2.26 (t, 4H, *J*= 7.3 Hz), 1.88-1.66 (m, 4H), 1.52-1.41 (m, 8H), 1.29 (s, 6H), 1.15-1.10 (m, 2H), 0.98-0.88 (m, 2H), 0.89 (d, 12H, *J*= 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 211.47, 141.97, 139.51, 129.28, 126.45, 72.53, 45.02, 43.11, 42.69, 38.36, 30.26, 24.57, 23.63, 22.58, 21.72. HRMS (LSIMS, nba): Calcd. for $C_{35}H_{55}O_3$ (MH^+): 523.4151, found: 523.4144.

5.1.h. Synthesis of 2,10-Dimethyl-6-oxo-2,10-diphenyl-undecanedioic acid



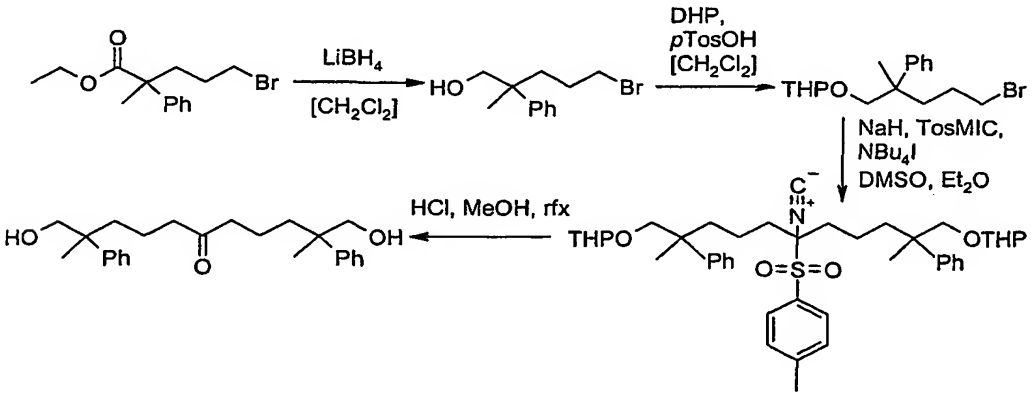
2,10-Dimethyl-6-oxo-2,10-diphenyl-undecanedioic acid diethyl ester

To a solution of ethyl 5-bromo-2-methyl-2-phenyl-pentanoate (25 g, 75.25 mmol), tetra-*n*-butylammonium iodide (2.78 g, 7.53 mmol), and *p*-toluenesulphonylmethyl isocyanide (TosMIC, 7.34 g, 37.63 mmol) in anhydrous DMSO (400 mL) and anhydrous diethyl ether (150 mL) was added sodium hydride (60% dispersion in mineral oil, 3.80 g, 95 mmol) at rt under N_2 atmosphere. The reaction mixture was stirred for 24 h at rt, then carefully hydrolized with ice-water (600 mL), and extracted with diethyl ether (2 × 300 mL). The organic layer was washed with brine (2 × 300 mL) dried over anhydrous $MgSO_4$, concentrated in vacuo to furnish crude 2,10-dimethyl-6-isocyano-6-(4-tolyl-sulfonyl)-2,10-diphenyl-undecanedioic acid diethyl ester (28 g) as a brown oil. A solution of this crude intermediate (25 g) was dissolved in CH_2Cl_2 (500 mL) and concd. HCl (140 mL) and stirred for 2 h at rt. The reaction mixture was diluted with water (500 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined layers were washed with saturated $NaHCO_3$ solution (150 mL), and brine (150 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude oil was purified by flash chromatography (silica gel, ethyl acetate/hexanes = 1/20, 1/10) to furnish 2,10-dimethyl-6-oxo-2,10-diphenyl-undecanedioic acid diethyl ester (9.5 g, 50.3 %) as a light yellowish oil. ^1H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 7.40 - 7.10 (m, 10 H), 4.20 - 4.05 (m, 4 H), 2.38 (m, 4 H), 2.05 - 1.80 (m, 4 H), 1.60 (s, 6 H), 1.50 - 1.20 (m, 4 H), 1.22 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 210.24, 176.06, 143.71, 128.42, 126.72, 125.97, 60.83, 50.13, 42.97, 38.91, 22.73, 22.47, 19.09, 14.13. HRMS (LSIMS, nba): Calcd. for $C_{29}H_{39}O_5$ (MH^+): 467.2797, found: 467.2772.

2,10-Dimethyl-6-oxo-2,10-diphenyl-undecanedioic acid

To a homogenous solution of KOH (85%, 7.17 g, 108.90 mmol) in water (15 mL) and ethanol (45 mL) was added 2,10-dimethyl-6-oxo-2,10-diphenyl-undecanedioic acid diethyl ester (14.5 g, 31.12 mmol). The reaction solution was heated to reflux for 6 h. The ethanol was removed in reduced pressure and the residue was diluted with water (300 mL). The solution was acidified with concd. HCl (18 mL) to pH 1 and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and purified by flash chromatography (silica gel, ethyl acetate/hexanes = 1/20, 1/10, 1/2) to furnish 2,10-dimethyl-6-oxo-2,10-diphenyl-undecanedioic acid (4 g, 31.4 %) as a white solid. Mp.: 44 - 46 °C. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 10.25 (br, 2 H), 7.35 - 7.22 (m, 10 H), 2.32 (m, 4 H), 1.94 - 1.86 (m, 4 H), 1.57 (s, 6 H), 1.51 - 1.22 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 210.64, 182.66, 142.69, 128.66, 127.18, 126.29, 50.07, 42.97, 38.62, 22.20, 19.11. HRMS (LSIMS, nba): Calcd. for $C_{25}H_{31}O_5$ (MH^+): 411.2171, found: 411.2144.

5.1.i. Synthesis of 1,11-Dihydroxy-2,10-dimethyl-2,10-diphenyl-undecan-6-one



5-Bromo-2-methyl-2-phenyl-pentan-1-ol

Methanol (5.24 g, 164 mmol) was added drop-wise to a stirred suspension of $LiBH_4$ (3.45 g, 150 mmol) in anhydrous CH_2Cl_2 (150 mL) under N_2 atmosphere. After the addition of ethyl 5-bromo-2-methyl-2-phenyl-pentanoate (23.70 g, 106 mmol), the reaction mixture was heated to reflux overnight. The reaction mixture was cooled to 5 °C and hydrolyzed

with ice (ca. 30 g) and NH_4Cl solution (150 mL) for 1 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with NH_4Cl solution (3 × 100 mL), dried over $MgSO_4$ and concentrated in vacuo to furnish 5-bromo-2-methyl-2-phenyl-pentan-1-ol (20 g, 96.8 %) as an oil. ^1H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 7.34 - 7.14 (m, 5 H), 3.60 (m, 1 H), 3.48 (m, 1 H), 3.29 (t, J = 6.0 Hz, 2 H), 1.96 - 1.44 (m, 5 H), 1.32 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 144.25, 128.59, 126.71, 126.41, 72.44, 43.15, 37.06, 34.64, 27.58, 21.61. HRMS (LSIMS, nba): Calcd. for $C_{12}H_{16}Br$ ($MH^+ - H_2O$): 239.0435, found: 239.0444.

2-(5-Bromo-2-methyl-2-phenyl-pentyloxy)-tetrahydropyran

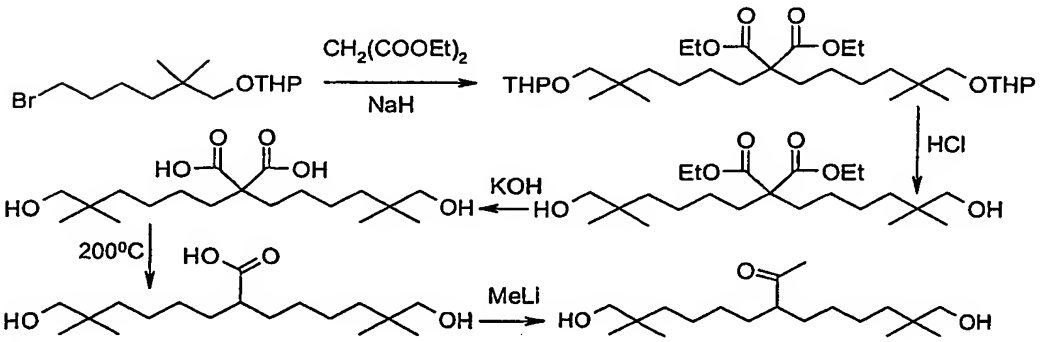
Under N_2 atmosphere, 3,4-dihydro-2*H*-pyran (8.19 g, 98 mmol) was added dropwise to a stirred solution of 5-bromo-2-methyl-2-phenyl-pentan-1-ol (20 g, 78 mmol) at -5 °C. The reaction mixture was allowed to warm to rt and stirred for 5 h. The solution was filtered through aluminum oxide (100 g), which was washed with CH_2Cl_2 (500 mL). The filtrate was concentrated in vacuo to furnish 2-(5-bromo-2-methyl-2-phenyl-pentyloxy)-tetrahydropyran (25.23 g, 96.2 %) as an oil. ^1H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 7.26 - 7.08 (m, 5 H), 4.45 (m, 1 H), 3.72 (m, 1 H), 3.58 (m, 1 H), 3.35 - 3.05 (m, 2 H), 3.28 (t, J = 6.6, 2 H), 1.95 - 1.39 (m, 10 H), 1.25 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 145.37, 128.14, 126.51, 126.03, 99.06, 98.92, 61.91, 61.80, 41.82, 41.74, 37.58, 37.43, 34.65, 30.61, 27.88, 25.58, 23.03, 22.89, 19.39, 19.32. HRMS (HR, LSIMS, nba): Calcd. for $C_{17}H_{26}O_2Br$ (MH^+): 341.1116, found: 341.1127.

1,11-Dihydroxy-2,10-dimethyl-2,10-diphenyl-undecan-6-one

To a solution of 2-(5-bromo-2-methyl-2-phenyl-pentyloxy)-tetrahydropyran (25 g, 74.18 mmol), tetra-*n*-butylammonium iodide (3.0 g, 8.16 mmol), and *p*-toluenesulfonyl-methyl isocyanide (TosMIC, 7.23 g, 37.09 mmol) in anhydrous DMSO (350 mL) and anhydrous diethyl ether (100 mL) was added sodium hydride (60% dispersion in mineral oil, 3.73 g, 1.26 mmol) at rt under N_2 atmosphere. The reaction mixture was allowed to stir for 24 h at this temperature, then was carefully hydrolized with ice and water (600 mL) and extracted with diethyl ether (2 × 300 mL). The combined organic layers were washed with brine (2 × 300 mL), dried over $MgSO_4$, and concentrated in vacuo to furnish 6-isocyano-6-(4-tolyl-sulfonyl)-2,10-dimethyl-2,10-diphenyl-11-(tetrahydropyran-2-yloxy)-undecanyloxy-tetrahydropyran (28 g) as a brown oil. A solution of this crude intermediate (28 g, 41.12 mmol) was dissolved in methanol (500 mL), concd. HCl (60 mL), and water (120 mL) and heated to reflux for 3 h. The reaction mixture was poured into CH_2Cl_2 (300 mL) and ice and

water (300 g). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (3 × 150 mL) and brine (150 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude oil was purified by flash chromatography (silica gel; hexanes, then ethyl acetate/hexanes = 1/20, 1/10, 1/2, 1/1) to furnish 1,11-dihydroxy-2,10-dimethyl-2,10-diphenyl-undecan-6-one (5.3 g, 34 %) as a light yellowish oil. ^1H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 7.38 - 7.30 (m, 8 H), 7.26 - 7.18 (m, 2 H), 3.62 (d, J = 10.5 Hz, 2 H), 3.48 (d, J = 10.5 Hz, 2 H), 2.25 (m, 6 H) 1.76 - 1.64 (m, 2 H), 1.58 - 1.16 (m, 6 H), 1.32 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 211.43, 144.84, 128.32, 126.58, 126.03, 71.79, 43.11, 42.89, 37.61, 21.68, 18.12. HRMS (LSIMS, nba): Calcd. for $C_{25}H_{33}O_2$ (MH^+ - H_2O): 365.2481, found: 365.2482.

5.1.j. Synthesis of 9-Hydroxy-3-(6-hydroxy-5,5-dimethyl-hexyl)-8,8-dimethyl-nonan-2-one



2,2-*Bis*-[5,5-dimethyl-6-(tetrahydropyran-2-yloxy)-hexyl]-malonic acid diethyl ester

Under nitrogen atmosphere, to a solution of 2-(6-bromo-2,2-dimethyl-hexyloxy)-tetrahydropyran (17.6 g, 60 mmol) and diethyl malonate (4.8 g, 30 mmol) in anhydrous DMSO (145 mL) was added sodium hydride (60 % dispersion in mineral oil, 2.88 g, 72 mmol) under cooling with a water-bath. Tetra-*n*-butylammonium iodide (2.1 g, 3.6 mmol) was then added. The mixture was stirred for 16 h at room temperature. Water (140 mL) was added carefully to the reaction mixture under cooling with water-bath. The product was extracted with diethyl ether (3 × 60 mL) and the combined organic layers were washed with water (4 × 50 mL) and brine (50 mL). The solution was dried over sodium sulfate and concentrated in vacuo to give 2,2-*bis*-[5,5-dimethyl-6-(tetrahydropyran-2-yloxy)-hexyl]-malonic acid diethyl ester (17.3 g, 82.3 %) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 4.41 (t, J = 3.1 Hz, 2H), 4.01 (q, J = 7.0 Hz, 4 H), 3.82 - 3.70 (m, 2 H), 3.50 - 3.30 (m, 4 H), 2.87 (d, J = 9.1 Hz, 2 H), 1.80 - 1.35 (m, 16 H), 1.30 - 0.95 (m, 18 H), 0.88 - 0.74 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 172.0, 99.1, 76.6, 61.9, 60.9, 57.6, 39.2, 34.3, 32.3, 30.7, 25.7, 25.0, 24.6, 24.6, 24.3, 19.5, 14.2.

2,2-*Bis*(6-hydroxy-5,5-dimethyl-hexyl)-malonic acid diethyl ester

A solution of 2,2-*bis*-[5,5-dimethyl-6-(tetrahydropyran-2-yloxy)-hexyl]-malonic acid diethyl ester (2.92 g, 5mmol) in concentrated HCl (2.4 mL) and water (1.6 mL) was refluxed for 1 h. Ethanol (8.2 mL) was added and the reaction mixture was heated to reflux for 3 h. The reaction mixture was diluted with water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), and dried over Na_2SO_4. The solution was concentrated to furnish 2,2-*bis*(6-hydroxy-5,5-dimethyl-hexyl)-malonic acid diethyl ester (1.74 g, 84 %). ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 4.13 (q, J = 7.2 Hz, 4 H), 3.25 (s, 4 H), 2.42 (s, 2 H), 1.90 - 1.75 (m, 4 H), 1.30 - 1.12 (m, 18 H), 0.84 (s, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 172.0, 71.7, 60.9, 57.4, 38.2, 34.9, 32.1, 24.8, 24.0, 23.7, 14.0.

2,2-*Bis*-(6-hydroxy-5,5-dimethyl-hexyl)-malonic acid

To a stirred solution of KOH (4.83 g, 75 mmol) in water (4.2 mL) and ethanol (15 mL) was added 2,2-*bis*(6-hydroxy-5,5-dimethyl-hexyl)-malonic acid diethyl ester (15 g). The reaction mixture was heated to reflux for 14 h, then concentrated *in vacuo*, and extracted with chloroform. The aqueous layer was acidified with HCl until pH 1 and extracted with diethyl ether (3 × 50 mL). The ethereal solution was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford get 2,2-*bis*-(6-hydroxy-5,5-dimethyl-hexyl)-malonic acid (7.8 g, 82.3 %) as a yellow solid. ^{1}H NMR (300 MHz, CD_3OD/TMS): δ (ppm)

4.86 (s, 4 H), 3.22 (s, 4 H), 1.9 - 1.8 (m, 4 H), 1.36 - 1.10 (m, 12 H), 0.84 (s, 12 H). ^{13}C NMR (75 MHz, CD_3OD/TMS): δ (ppm) 176.0, 72.0, 58.7, 39.8, 36.0, 34.1, 26.5, 25.5, 24.5. Mp.: 178 - 180 °C.

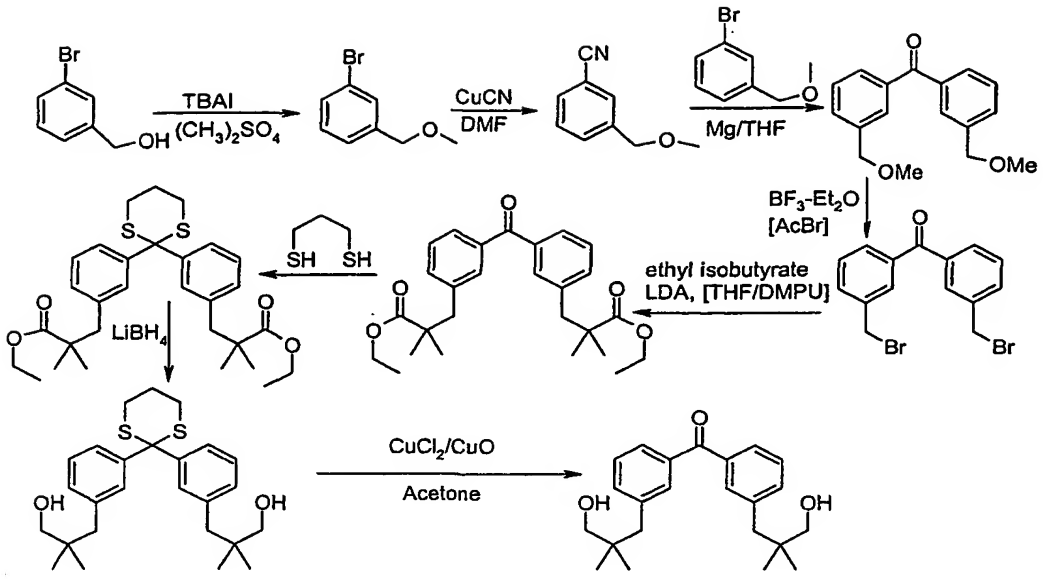
8-Hydroxy-2-(6-hydroxy-5,5-dimethyl-hexyl)-7,7-dimethyl-octanoic acid

2,2-*Bis*-(6-hydroxy-5,5-dimethyl-hexyl)-malonic acid was heated to 200 °C using an oil-bath. This temperature was kept for 30 minutes until the effervescence ceased. 8-Hydroxy-2-(6-hydroxy-5,5-dimethyl-hexyl)-7,7-dimethyl-octanoic acid was obtained as an oil (4.04 g, 98 %). ^1H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 4.88 (s, 3 H), 3.22 (s, 4 H), 2.29 (m, 1 H), 1.70 - 1.40 (m, 4 H), 1.4 - 1.1 (m, 12 H), 0.84 (s, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 180.5, 72.1, 47.1, 39.9, 36.0, 33.8, 29.7, 25.0, 24.6.

9-Hydroxy-3-(6-hydroxy-5,5-dimethyl-hexyl)-8,8-dimethyl-nonan-2-one

8-Hydroxy-2-(6-hydroxy-5,5-dimethyl-hexyl)-7,7-dimethyl-octanoic acid (1.0 g, 3.16 mmol) was dissolved in THF (40 mL) and cooled in an ice-water bath. Methyl lithium (27 mL) was then added at once. The reaction was continued for 2 h at 0 °C. The reaction mixture was poured into dilute hydrochloric acid (5 mL concentrated hydrochloric acid in 60 mL water). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo to give the crude product (1.0 g). The crude product was purified by column chromatography (hexanes : ethyl acetate = 4 : 1, then 1 : 1) to give 9-hydroxy-3-(6-hydroxy-5,5-dimethyl-hexyl)-8,8-dimethyl-nonan-2-one (0.41 g, yield 41 %) and 7-(1-hydroxy-1-methylethyl)-2,2,12,12-tetramethyltridecan-1,13-diol (0.4 g, 38 %, not shown) as a by-product. ^1H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 3.46 (s, 4 H), 2.65 - 2.50 (m, 1 H), 2.28 (s, 3 H), 2.60 (br., 2 H), 1.82 - 1.50 (m, 4 H), 1.50 - 1.25 (m, 12 H), 1.02 (s, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm) 213.4, 71.7, 53.2, 38.3, 34.9, 31.6, 28.7, 28.3, 23.8. HRMS (LSIMS, nba): Calcd. for $C_{19}H_{39}O_3$ (MH^+): 315.2899, found: 315.2866.

5.1.k. Synthesis of *Bis*[3-(3-hydroxy-2,2-dimethylpropyl)phenyl]methanone



3-{3-[3-(2-Ethoxycarbonyl-2-methyl-propyl)-benzoyl]-phenyl}-2,2-dimethyl-propionic acid ethyl ester

A solution of lithium diisopropylamide (LDA, 2.0 M in heptane/THF, ethyl benzene, 42.2 mL, 84.4 mmol) was added drop-wise to a solution of ethyl isobutyrate (9.78 g, 84.3 mmol) in anhydrous THF (30 mL) at – 78 °C. The mixture was allowed to stir at – 78 °C for 1 h, before 3,3'-*bis*(bromomethyl)benzophenone ((prepared according to Shultz, D.A.; Fox, M. A. *J. Am. Chem. Soc.* **1989**, *16*, 6311, from 3-bromobenzyl methyl ether (Friedman, L.; Shechter, H. *J. Org. Chem.* **1961**, *26*, 2522), 10.34 g, 28.1 mmol) was added, followed by addition of DMPU (2.7 g, 17 mmol). The mixture was stirred for 30 min at – 78 °C, allowed to warm to rt, and stirred for 30 min. The THF was removed under reduced pressure and the residue was diluted with saturated NH_4Cl (280 mL). The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (200 mL), 5 % HCl (100 mL), and saturated $NaHCO_3$ solution (50 mL), then dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to furnish 3-{3-[3-(2-ethoxycarbonyl-2-methyl-propyl)-benzoyl]-phenyl}-2,2-dimethyl-propionic acid ethyl ester (11.0 g, 90%) as an oil. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm): 7.8 - 7.2 (m, 8 H), 3.98 (q, *J*

= 6.9 Hz, 4 H), 2.83 (s, 4 H), 1.2 - 0.8 (m, 18 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 196.5, 176.8, 138.1, 137.2, 134.0, 131.4, 128.1, 127.7, 60.3, 45.7, 43.3, 24.8, 13.9.

3-(3-{2-[3-(2-Ethoxycarbonyl-2-methyl-propyl)-phenyl]-[1,3]dithian-2-yl}-phenyl)-2,2-dimethyl-propanoic acid ethyl ester

To a solution of 3-{3-[3-(2-ethoxycarbonyl-2-methyl-propyl)-benzoyl]-phenyl}-2,2-dimethyl-propionic acid ethyl ester (6.2 g, 14 mmol) in dichloromethane (100 mL) was added 1,3-propanedithiol (1.9 g, 17.5 mmol) and borontrifluoride etherate (0.52 mL). The solution was stirred at room temperature overnight and 5 % sodium hydroxide solution (17.5 mL) was added. The organic layer was separated, washed with water (50 mL), dried over sodium sulfate, and evaporated to afford 3-(3-{2-[3-(2-ethoxycarbonyl-2-methyl-propyl)-phenyl]-[1,3]dithian-2-yl}-phenyl)-2,2-dimethyl-propanoic acid ethyl ester (6.5 g, 86 %) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): 7.58 - 6.96 (m, 8 H), 4.10 (q, J = 7.2 Hz, 4 H), 2.85 (s, 4 H), 2.76 (t, J = 5.6 Hz, 4 H), 1.98 (m, 2 H), 1.25 - 1.14 (m, 18 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 177.2, 142.2, 138.1, 131.1, 129.3, 127.8, 127.3, 60.4, 46.2, 43.5, 29.4, 24.9, 24.5, 14.1.

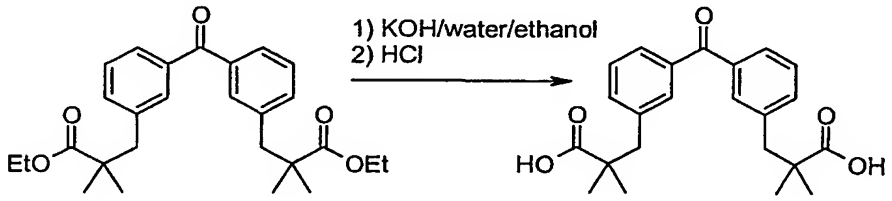
3-(3-{2-[3-(3-Hydroxy-2,2-dimethyl-propyl)-phenyl]-[1,3]dithian-2-yl}-phenyl)-2,2-dimethyl-propan-1-ol

To a suspension of $LiBH_4$ (0.78 g, 33 mmol) in dichloromethane (55 mL) was added methanol (1.04 g, 33 mmol) at rt. After the addition of 3-(3-{2-[3-(2-ethoxycarbonyl-2-methyl-propyl)-phenyl]-[1,3]dithian-2-yl}-phenyl)-2,2-dimethyl-propanoic acid ethyl ester (6.5 g, 12.2 mmol), the reaction mixture was heated to reflux for 6 h. After cooling to rt, saturated ammonium chloride solution (20 mL) and dichloromethane (15 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo to afford crude 3-(3-{2-[3-(3-hydroxy-2,2-dimethyl-propyl)-phenyl]-[1,3]dithian-2-yl}-phenyl)-2,2-dimethyl-propan-1-ol (4.66 g, 85 %) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): 7.6 - 6.8 (m, 8 H), 3.63 (s, 4 H), 3.16 (s, 4 H), 2.95 - 2.60 (m, 4 H), 2.0 - 1.8 (m, 2 H), 1.61 (s, 2 H), 0.75 (s, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 142.4, 139.2, 131.7, 128.9, 128.1, 127.0, 71.1, 44.9, 43.7, 36.7, 29.6, 27.3, 24.2.

***Bis*-[3-(3-hydroxy-2,2-dimethylpropyl)-phenyl]-methanone**

A three-necked flask fitted with a magnetic stirring bar, a condenser, and a pressure-equalizing dropping funnel was charged with copper(II)oxide (0.96 g, 12 mmol), anhydrous copper(II)chloride (3.2 g, 24 mmol) and acetone (80 mL). The resulting suspension was brought to reflux with vigorous stirring, and a solution of 3-(3-{2-[3-(3-hydroxy-2,2-dimethyl-propyl)-phenyl]-[1,3]dithian-2-yl}-phenyl)-2,2-dimethyl-propan-1-ol (4.44 g, 10 mmol) in acetone (20 mL) and DMF (1.2 mL) was added over five min. Reflux temperature was maintained for 90 min. The reaction mixture was cooled and filtered. The insoluble materials were washed with dichloromethane (3 × 20 mL) and the combined organic solutions were washed with aqueous 2 N sodium carbonate solution (50 mL), dried over sodium sulfate, and filtered. Concentration in vacuo gave crude *bis*-[3-(3-hydroxy-2,2-dimethylpropyl)-phenyl]-methanone, which was purified by chromatography on silica (hexanes : acetone = 4:1) to yield an oil (2.5 g, 70.6 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): 7.68 - 7.30 (m, 8 H), 3.31 (s, 4 H), 3.03 (s, 2 H), 2.65 (s, 4 H), 0.88 (s, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 197.4, 139.1, 137.0, 134.6, 131.9, 127.8, 127.6, 70.4, 44.1, 36.3, 23.8. HRMS (LSIMS, gly): Calcd. for $C_{23}H_{31}O_3$ (MH^+): 355.2273, found: 355.2273.

5.1.l. Synthesis of 3-{3-[3-(2-Carboxy-2-methylpropyl)-benzoyl]-phenyl}-2,2-dimethyl-propanoic acid

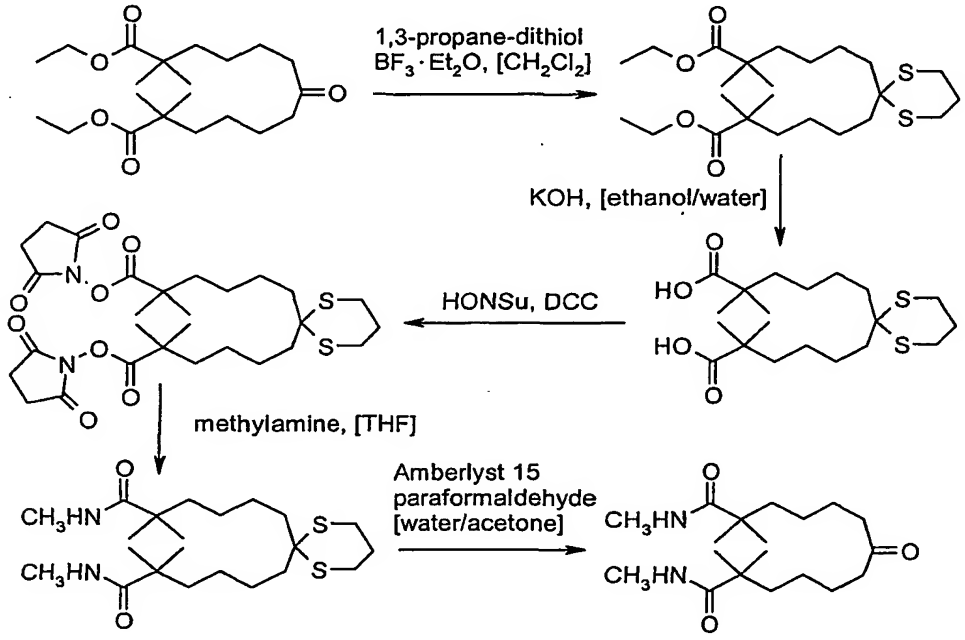


3-{3-[3-(2-Carboxy-2-methylpropyl)benzoyl]-phenyl}-2,2-dimethyl-propanoic acid

To a solution of potassium hydroxide (1.57 g, 28 mmol) in water (1.5 mL) and absolute ethanol (5 mL) was added 3-{3-[3-(2-ethoxycarbonyl-2-methyl-propyl)-benzoyl]-phenyl}-2,2-dimethyl-propionic acid ethyl ester (4.38 g, 10 mmol) in portions. The mixture was heated to reflux for 3 h and the ethanol was distilled off under reduced pressure on a water-bath. The residual aqueous solution was extracted with chloroform (2 × 50 mL), then cooled with an ice-bath, and acidified with hydrochloric acid to pH 1. The mixture was extracted with diethyl ether (3 × 50 mL). The ethereal extracts were dried over sodium

sulfate and concentrated in vacuo to give 3-{3-[3-(2-carboxy-2-methylpropyl)benzoyl]-phenyl}-2,2-dimethyl-propanoic acid (3.88 g, 100 %) as a solid. Mp.: 46 - 48 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): 7.8 - 7.2 (m, 8 H), 2.83 (s, 4 H), 1.25 (s 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 198.02, 184.0, 139.2, 137.3, 134.5, 129.5, 128.4, 128.3, 127.6, 43.8, 24.7. HRMS (LSIMS, gly): Calcd. for $C_{23}H_{27}O_5$ (MH^+): 383.1858, found: 383.1858.

5.1.m. Synthesis of 2,2,12,12-Tetramethyl-7-oxo-tridecanedioic acid *bis*-methylamide



6-[2-(5-Ethoxycarbonyl-5-methyl-hexyl)-[1,3]dithian-2-yl]-2,2-dimethyl-hexanoic acid ethyl ester

Under N_2 atmosphere, to a solution of 2,2,12,12-tetramethyl-7-oxo-tridecanedioic acid diethyl ester (1.0 g, 2.70 mmol) and 1,3-propanedithiol (361 mg, 361 µL, 3.24 mmol) in dichloromethane (20 mL; dried with Aluminum oxide, activated, neutral, Brockmann I) was added boron trifluoride diethyl etherate (100 µL) at rt. The reaction mixture was stirred for 3 h, diluted with dichloromethane (100 mL), and extracted with 5 % NaOH solution (100 mL) and water (75 mL). The organic phase was dried over $MgSO_4$, concentrated in vacuo, and dried in high vacuo to furnish 6-[2-(5-ethoxycarbonyl-5-methyl-hexyl)-[1,3]dithian-2-yl]-2,2-dimethyl-hexanoic acid ethyl ester (1.0 g, 80 %) as a yellowish oil. ^{1}H

NMR (300 MHz, $CDCl_3$/TMS): δ (ppm): 4.11 (q, 4 H, J = 7.1), 2.79 (t, 4 H, J = 5.6), 1.94 (m, 2 H), 1.84 (m, 4 H), 1.54 (m, 4 H), 1.39 (m, 4 H), 1.24 (t, 6 H, J = 7.1), 1.30 – 1.20 (m, 4 H), 1.16 (s, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm): 178.08, 60.33, 53.32, 42.27, 40.69, 38.28, 26.14, 25.67, 25.28, 24.71, 14.41. HRMS (LSIMS, nba): Calcd. for $C_{24}H_{45}S_2O_4$ (MH^+): 461.2759, found 461.2774.

6-[2-(5-Carboxy-5-methyl-hexyl)-[1,3]dithian-2-yl]-2,2-dimethyl-hexanoic acid

A solution of 6-[2-(5-ethoxycarbonyl-5-methyl-hexyl)-[1,3]dithian-2-yl]-2,2-dimethyl-hexanoic acid ethyl ester (870 mg, 1.89 mmol) and potassium hydroxide (85 %, 750 mg, 11.33 mmol) in ethanol (16 mL) and water (4 mL) was heated under reflux for 3 h. The reaction mixture was diluted with water (100 mL) and acidified to pH 4 with 1 N HCl (8 mL). The emulsion was extracted with dichloromethane (3 × 75 mL). The combined organic phases were washed with water (50 mL), dried over $MgSO_4$, concentrated in vacuo, and dried in high vacuo to furnish 6-[2-(5-carboxy-5-methyl-hexyl)-[1,3]dithian-2-yl]-2,2-dimethyl-hexanoic acid (730 mg, 95 %) as a viscous, yellowish oil. ^1H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm): 2.80 (m, 4 H), 1.94 (m, 2 H), 1.85 (m, 4 H), 1.56 (m, 4 H), 1.41 (m, 4 H), 1.30 (m, 4 H), 1.19 (s, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm): 185.08, 53.36, 42.28, 40.52, 38.27, 26.18, 25.69, 25.23, 25.11, 24.73. HRMS (LSIMS, nba): Calcd. for $C_{20}H_{37}O_4S_2$ (MH^+): 405.2133, found: 405.2115.

2,2-Dimethyl-6-[2-(5-methyl-5-methylcarbamoyl-hexyl)-[1,3]dithian-2-yl]-hexanoic acid methylamide

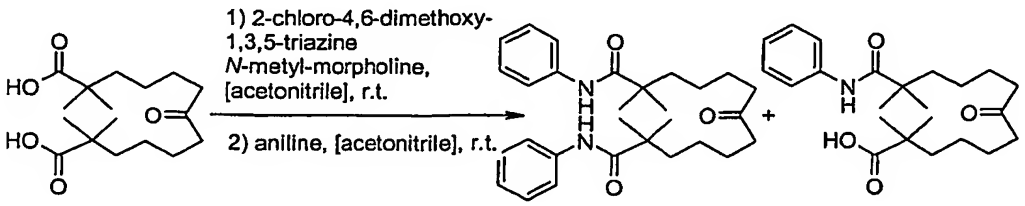
Under N_2 atmosphere, to a solution of 6-[2-(5-carboxy-5-methyl-hexyl)-[1,3]dithian-2-yl]-2,2-dimethyl-hexanoic acid (280 mg, 0.67 mmol) and *N*-hydroxysuccinimide (170 mg, 1.47 mmol) in dichloromethane (5 mL; dried with Aluminum oxide, neutral, Brockmann I) was added dicyclohexyl carbodiimide (305 mg, 1.47 mmol). The reaction mixture was stirred and rt for 2 h, the urea was removed by filtration and washed with dichloromethane (2 mL). The filtrate was concentrated in vacuo and dried in high vacuo to give crude 6-{2-[5-(2,5-dioxo-pyrrolidin-1-yloxycarbonyl)-5-methyl-hexyl]-[1,3]dithian-2-yl}-2,2-dimethyl-hexanoic acid 2,5-dioxo-pyrrolidin-1-yl ester (500 mg, 125 %) as a foamy, yellow oil. Under N_2 atmosphere, to a solution of this crude intermediate (370 mg, 0.62 mmol) in anhydrous THF (10 mL) was added a solution of methylamine in anhydrous THF (5 mL, 10 mmol, 2.0 M in THF), resulting in the immediate formation of a white precipitate. The reaction mixture was stirred at rt for 1.5 h, then diluted with dichloromethane (100 mL), and

extracted with saturated $NaHCO_3$ solution (2 × 50 mL), water (50 mL), 1 N HCl (50 mL), and saturated NaCl solution. The organic phase was concentrated in vacuo and the residue purified by flash chromatography (silica, hexanes/ethyl acetate = 50/50, then 25/75, then 0/100) to furnish 2,2-dimethyl-6-[2-(5-methyl-5-methylcarbamoyl-hexyl)-[1,3]dithian-2-yl]-hexanoic acid methylamide (100 mg, 37 %) as a colorless oil. Mp.: 104 - 106 °C. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm): 5.92 (m br, 2 H), 2.81 (d, 6 H, J = 4.6), 2.78 (m, 4 H), 1.94 (m, 2 H), 1.82 (m, 4 H), 1.52 (m, 4 H), 1.37 (m, 4 H), 1.30 – 1.14 (m, 4 H), 1.17 (s, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm): 178.46, 53.23, 42.10, 41.32, 38.18, 26.56, 26.08, 25.62, 25.56, 25.16, 24.64. HRMS (LSIMS, nba): Calcd. for $C_{22}H_{43}N_2S_2O_2$ (MH^+): 431.2766, found: 431.2762.

2,2,12,12-Tetramethyl-7-oxo-tridecanedioic acid *bis*-methylamide

A suspension of 2,2-dimethyl-6-[2-(5-methyl-5-methylcarbamoyl-hexyl)-[1,3]dithian-2-yl]-hexanoic acid methylamide (3.30 g, 7.66 mmol), paraformaldehyde (6.9 g), and Amberlyst 15 (3.85 g) in acetone (100 mL) and water (10 mL) was heated to reflux for 16 h. The acetone was removed under reduced pressure, the reaction mixture was filtered, and the resin was washed with ethyl acetate (3 × 75 mL). The combined layers were extracted with saturated $NaHCO_3$ solution (30 mL) and saturated NaCl solution (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica; ethyl acetate, then ethyl acetate/ethanol = 50/50) to furnish 2,2,12,12-tetramethyl-7-oxo-tridecanedioic acid *bis*-methylamide (2.45 g, 94 %) as a colorless, viscous oil that solidified on standing. Mp.: 91.5 – 93.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm): 6.05 (d br., 2 H, J = 4.6), 2.78 (d, 6 H, J = 4.6), 2.36 (t, 4 H, J = 7.3), 1.58 – 1.45 (m, 8 H), 1.27 – 1.12 (m, 4 H), 1.15 (s, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm): 211.50, 178.43, 42.56, 41.99, 41.03, 26.52, 25.48, 24.48, 24.20. HRMS (LSIMS, nba): Calcd. for $C_{19}H_{37}N_2O_3$ (MH^+): 341.2804, found: 341.2804.

5.1.n. Synthesis of 2,2,12,12-Tetramethyl-7-oxo-tridecanedioic acid *bis*-phenylamide



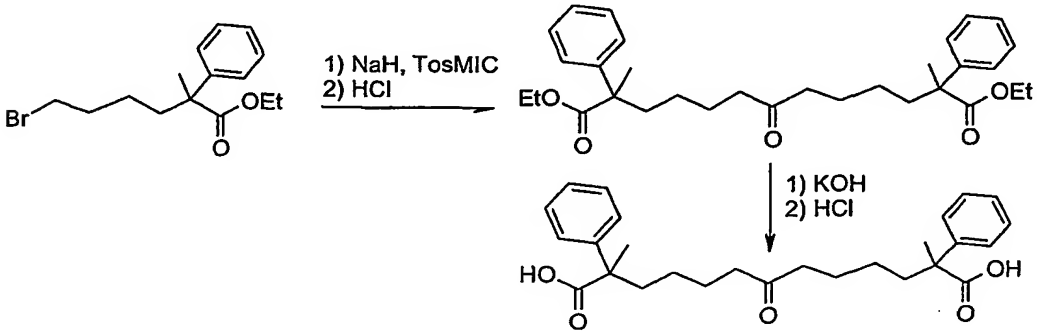
2,2,12,12-Tetramethyl-7-oxo-tridecanedioic acid *bis*-phenylamide

Under N_2 atmosphere, to a stirred solution of 2,2,12,12-tetramethyl-7-oxo-tridecanedioic acid (3.40 g, 10.9 mmol) in acetonitrile (50 ml) was added *N*-methyl-morpholine (2.42 g, 2.63 ml, 23.9 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (4.20 g, 23.9 mmol) at rt. After 20 h, aniline (5.08 g, 5.0 ml, 54.5 mmol) was added and the reaction mixture was stirred for 26 h. The reaction mixture was diluted with ethyl acetate (100 mL) and extracted with ice-cold 1 N HCl (2 × 100 mL), saturated NaCl solution (100 mL), saturated $NaHCO_3$ solution (2 × 100 mL), and saturated NaCl solution (100 mL). The organic layer was dried over $MgSO_4$, concentrated in vacuo, and dried in high vacuo to give a viscous, crude oil (4.50 g). 2,2,12,12-Tetramethyl-7-oxo-tridecanedioic acid *bis*-phenylamide and 2,2,12-trimethyl-7-oxo-12-phenylcarbamoyl-tridecanoic acid were isolated from this crude product mixture by flash chromatography (silica; chloroform, then chloroform/acetone = 98/2, then chloroform/acetone = 95/5). Additional purification of 2,2,12,12-tetramethyl-7-oxo-tridecanedioic acid *bis*-phenylamide by crystallization (1.0 g oil in ca. 7.5 ml hexanes/chloroform/ethanol = 10/4/1) was necessary to give the clean *bis*-amide (290 mg, 6 %) as a white solid. Mp.: 113 – 114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): 7.52 (d, 2 H, J = 7.5), 7.50 (s, 2 H), 7.27 (t, 4 H, J = 7.5), 7.07 (t, 2 H, J = 7.5), 2.34 (t, 4 H, J = 7.3), 1.64 – 1.44 (m, 8 H), 1.34 – 1.14 (m, 4 H), 1.24 (s, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 211.31, 176.08, 138.09, 128.93, 124.28, 120.36, 42.96, 42.84, 41.13, 25.58, 24.53, 24.20. HRMS (LSIMS, nba): Calcd. for $C_{29}H_{40}N_2O_3$ (MH^+): 465.3118, found: 465.3129.

2,2,12-Trimethyl-7-oxo-12-phenylcarbamoyl-tridecanoic acid

Viscous oil (1.15 g, 25 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): 8.90 (m br., 1 H), 7.57 (s br, 1 H), 7.51 (d, 2 H, J = 7.9), 7.28 (m, 2 H), 7.08 (t, 1 H, J = 7.3), 2.38 (t, 2 H, J = 7.2), 2.36 (t, 2 H, J = 7.2 H), 1.53 (m, 8 H), 1.34 – 1.20 (m, 4 H), 1.26 (s, 6 H), 1.16 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 211.54, 183.74, 176.28, 138.02, 128.92, 124.35, 120.46, 42.97, 42.55, 42.53, 42.06, 41.12, 40.21, 25.56, 25.05, 24.55, 24.52, 24.21, 24.17. HRMS (LSIMS, nba): Calcd. for $C_{23}H_{36}NO_4$ (MH^+): 390.2644, found: 390.2650.

5.1.o. Synthesis of 7-Oxo-2,12-dimethyl-2,12-diphenyl-tridecanedioic acid



7-Oxo-2,12-dimethyl-2,12-diphenyl-tridecanedioic acid diethyl ester

Under N_2-atmosphere, to a solution of ethyl 6-bromo-2-methyl-2-phenyl-hexanoate (9.59 g, 30 mmol) in DMSO (50 mL, dried over 4 Å molecular sieves) was added *p*-toluenesulphonylmethyl isocyanide (TosMIC, 3.02 g, 15 mmol), sodium hydride (60 % w/w in mineral oil, 1.44 g, 36 mmol), and tetra-*n*-butyl ammonium iodide (1.10 g, 3.0 mmol) under cooling with an ice-bath. After the addition, the reaction mixture was stirred for 96 h at rt, then cooled to 0 °C, and carefully hydrolyzed with water (100 mL). The product was extracted with dichloromethane (2 × 100 mL, 50 mL). The combined organic layers were washed with water (50 mL), dried over $MgSO_4$ and concentrated in *vacuo* to give an oil (30.0 g). To a solution of this oil (30.0 g) in CH_2Cl_2 (300 mL) was added concd. HCl (40 mL) and the reaction mixture was stirred for 2 h at rt. The solution was diluted with water (150 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (30 mL) and saturated NaCl solution (30 mL). The organic phases were dried over $MgSO_4$, concentrated in *vacuo* to give an oil (11.2 g). The product was purified by flash chromatography (silica; hexanes/ethyl acetate = 91/9) to furnish 7-oxo-2,12-dimethyl-2,12-diphenyl-tridecanedioic acid diethyl ester (5.0 g, 67 %) as a clear oil and 1.17 g (16%) of less pure fraction. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm) 7.40 - 7.10 (m, 10 H), 4.11 (q, J = 7.0 Hz, 4 H), 2.34 (t, J = 7.1 Hz, 4 H), 2.10 - 1.70 (m, 4 H), 1.6 - 1.4 (m, 10 H), 1.30 - 1.00 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm): 210.7, 176.0, 143.8, 128.2,

126.5, 125.8, 60.6, 50.0, 42.4, 38.9, 24.3, 24.1, 22.6, 14.0. HRMS (LSIMS, nba): Calcd. for $C_{31}H_{42}O_5$ (MH^+): 495.3110, found 495.3106.

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7-Oxo-2,12-dimethyl-2,12-diphenyl-tridecanedioic acid

To a solution of 7-oxo-2,12-dimethyl-2,12-diphenyl-tridecanedioic acid diethyl ester (3.93 g, 7.55 mmol) in ethanol (60 mL) was added a solution of KOH (4.0 g, 85%, 60 mmol) in water (10 mL). The reaction mixture was heated under reflux for 3 h and then
10 kept overnight at rt. The solution was concentrated under reduced pressure. The residue was dissolved in water (100 mL) and washed with ether (2 × 75 mL). The aqueous layer was acidified with concd. HCl (ca. 12 mL) until pH 1. The product was extracted with diethyl ether (3 × 75 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in *vacuo* to give 7-oxo-2,12-dimethyl-2,12-diphenyl-tridecanedioic acid as
15 an oil (3.0 g, 90 %). ^1H NMR (300 MHz, $CDCl_3$/TMS): δ (ppm): 7.40 - 7.10 (m, 10 H), 2.32 (t, J = 7.2 Hz, 4 H), 2.10 - 1.80 (m, 4 H), 1.6 - 1.45 (m, 10 H), 1.25 - 1.10 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ (ppm): 211.1, 182.5, 142.8, 128.4, 126.9, 126.0, 49.9, 42.3, 38.7, 24.2, 24.0, 22.3. HRMS (LSIMS, nba): Calcd. for $C_{27}H_{35}O_5$ (MH^+): 439.2484, found 439.2497.

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5.2. LDL-Cholesterol, HDL-Cholesterol and Triglyceride Levels in Male Sprague-Dawley Rats

Illustrative compounds of the invention are administered daily at a dose of 100
25 mg/kg to chow fed male Sprague-Dawley rats for seven days in the morning by oral gavage in 1.5% carboxymethylcellulose/0.2% Tween-20 (dosing vehicle). Animals are weighed daily. Animals are allowed free access to rodent chow and water throughout the study. After the seventh dose, animals are sacrificed in the evening and blood serum is assayed for lipoprotein cholesterol profiles, serum triglycerides, total cholesterol VLDL, LDL, and HDL
30 cholesterol, and the ratio of HDL cholesterol to that of VLDL plus LDL cholesterol, apolipoproteins A-I, C-II, C-III, and E by immunoelectrophoresis, and percent weight gain.

5.3. LDL-Cholesterol, HDL-Cholesterol and
35 **Triglyceride Levels in Obese Female Zucker Rats**

5.3.a. Experiment A

Dosing vehicle, Compound A (86 mg/kg of body weight) or troglitazone (120 mg/kg of body weight) is administered to eight week old female obese Zucker rats daily for seven days in the morning by oral gavage in 1.5% carboxymethylcellulose/0.2% Tween-20. Troglitazone is obtained commercially. Finely crushed tablets are suspended in vehicle for dosing. Orbital blood samples are obtained following a six-hour fast prior to the initial dose and also following the seventh dose.

Blood serum is assayed for total cholesterol and triglycerides, lipoprotein cholesterol profiles, VLDL plus LDL cholesterol combined (also referred to as apo B containing lipoprotein cholesterol or non-HDL cholesterol), HDL cholesterol, and the ratio of HDL cholesterol to that of VLDL plus LDL cholesterol, serum glucose, and non-esterified fatty acids, and percent weight gain.

5.3.b. Experiments B, C, D, & E

In a number of different experiments, illustrative compounds of the invention and troglitazone are administered daily at various doses to 10 week old chow fed obese female Zucker rats for 14 days in the morning by oral gavage in 1.5% carboxymethylcellulose/ 0.2% Tween-20 (dosing vehicle). Animals are weighed daily. Animals are allowed free access to rodent chow and water throughout the study. Blood glucose is determined after a 6-hour fast in the afternoon without anesthesia from a tail vein. Serum is also prepared from a blood sample subsequently obtained from the orbital venous plexus (with O_2/CO_2 anesthesia) prior to and after one week treatment and used lipid and insulin determinations.

At two weeks, blood glucose is again determined after a 6-hour fast without anesthesia from a tail vein. Soon thereafter, animals are sacrificed by CO_2 inhalation in the evening and cardiac blood serum is collected and assessed for various lipids and insulin. Body weight is determined daily prior to dosing and at the time of euthanasia. Blood glucose and serum insulin levels are determined from fasted rats just prior to and following one and two weeks of treatment. Percent liver to body weight is determined after two weeks of treatment at the time of sacrifice.

5.4. Lipoprotein Cholesterol Profile in LDL Receptor-Deficient Mice

Homozygous familial hypercholesterolemia is a rare human disease (~1/1,000,000) characterized by absent or defective LDL receptors, markedly elevated serum LDL cholesterol levels and very early and severe onset of atherosclerosis. The more common form of this disease in humans, heterozygous familial hypercholesterolemia , occurs in

about one in every 500 humans. Patients with the heterozygous form of this disease also present with elevated LDL levels and early onset of atherosclerosis.

The effect on LDL levels in a murine model of homozygous familial hypercholesterolemia can be studied according to the methods described in Ishibashi *et al.*, 1993, *J. Clin. Invest.* 92:883-893; Ishibashi *et al.*, 1994, *J. Clin. Invest.* 93:1885-1893, hereby expressly incorporated herein by reference. LDL receptor-deficient mice have elevated LDL cholesterol relative to wild type mice when fed a chow diet. When fed cholesterol-enriched diets, these mice develop atherosclerosis.

5.5. Synthesis of Non-Saponified and Saponified Lipids in Hepatocytes Isolated from a Male Sprague-Dawley Rat

Washout buffer containing; 149 mM sodium chloride, 9.2 mM sodium *N*-2-hyroxyethylpiperazine-*N*'-2-ethanesu!fonic acid, 1.7 mM fructose, 0.5 mM EGTA, 10 U/ mL heparin at pH 7.5 and digestion buffer containing; 6.7 mM potassium chloride, 143 mM sodium chloride, 9.2 mM sodium *N*-2-hyroxyethylpiperazine-*N*'-2-ethanesulfonic acid, 5 mM calcium chloride-dihydrate, 1.7 mM fructose, 0.2% bovine serum albumin, 100 U/ ml. collagenase Type 1, 93 U/ mL Hyaluronidase, 160 BAEE/ mL trypsin inhibitor at pH 7.5 were prepared. Solutions were oxygenate prior to perfusion. Wash buffer containing Dulbecco's Modified Eagle Medium (DMEM) containing 4.5 gm/L D-glucose, 2 mM GlutMax-1, 0.2% BSA, 5% fetal bovine serum (FBS), 12 nM insulin, 1.2 μM hydrocortisone and DMEM+HS solution containing DMEM, 2 mM GlutMax-l, 20 nM delta-aminolevulinic acid, 17.4 mM MEM non-essential amino acids, 20% EBS, 12 nM insulin and 1.2 μM hydrocortisone was prepared. DMEM- solution containing DMEM, 2 mM GlutMax-l, 20 nM delta-aminolevulinic acid and 17.4 mM MEM non-essential amino acids were prepared. Male Sprague-Dawley rats weighing 125-250 gms were maintained on a standard rodent chow diet and freely given water. On the evening prior to cell isolation, selected healthy animals were fed restricted. The rat was anesthetized with a 50 mg/kg intraperitoneal administration of sodium pentobarbital. Clotting was minimized with intraperitoneal administer of heparin at 1000 IU/kg body weight. The abdominal cavity was opened and the portal vein was surgical isolated. The angiocatheter was inserted into the portal vein at the genera! location of the lineal branch and connected to a perfusion pump, The in situ perfusion was performed at (~30 mL/min) with washout buffer, equilibrated with annosphere gases at a temperature of 37°C. The internal iliac artery was cut to allow pressure equilibration. The caustal area of the diaphragm was excised to provide access to the caudal vena cava and the aorta, using curved forceps both vessels were occluded. About

200 mL of buffer was needed to clear the liver. Digestion buffer was circulated at the same flow rate for about 7 minutes after the initial entry of digestion buffer into the liver, When the liver had significantly increased in size, and consistency, and started to leak perfusate the perfusion was discontinued. The liver was rinsed in situ with sterile saline and surgical removed from the animal to a sterile beaker. Additional digestion solution was dispensed into the beaker and cap with foil. The liver tissue was gently shaken using sterile forceps to free hepatocyte cells. Cells were filtered through presterilized stainless steels mesh sieves of pore sizes 250, 106 and 75 μm. Cells were diluted in with ice-cold wash buffer, pipetted successively to assist the disassociation of the cells and transferred to a 50 mL tube. The cells are centrifuged for about 4 minutes at 50 x g to form a loosely packed pellet. The supernatant is discarded and the pelleted cells were resuspend in ice-cold wash buffer. The washing procedure was repeated twice for a total of three washes. The final pellet was suspended in 50 mL of wash buffer and held on wet-ice. The viability and cell number was checked by diluting duplicate 100 μL aliquots of cell suspension with 400 μL of wash buffer and 500 μL of 0.4% trypan blue in isotonic buffer. The cell concentration was determined in several fields on the hemocytometer. The cell viability (those that exclude die) was 85% or greater. Cells were diluted in DMEM+HS to a final concentration to ensure plating at a density of 150,000 cells/cm^2 on collagen coated 6- or 12-well plates. Four hours after plating change the media was changed with DMEM- and culture overnight. Solutions of lovastatin, and illustrative compounds were prepared at 30 mM with DMSO. To obtain a compound solution mixtures were vortexed and sonicated.

To evaluate the effect of reference and illustrative compounds on saponified and non-saponifed lipid synthesis, the monolayer cultures were exposed to compounds formulated in DMEM- containing ^{14}C-acetate. All cells were exposed to 1% DMSO. Metabolic labeling with ^{14}C-acetate continued for 4 hr at 37°C. After labeling, cells were washed twice with 1 mL of PBS followed by lysing in 1 mL deionized water. Cells were scraped from the dishes and transferred to glass tubes at which point they were sonicated. 2.5 mL of 2:1 chloroform/methanol mixture was added followed by 1.5 mL of Phosphate Buffered Saline (PBS). To correct for extraction efficiency in the upcoming extractions, 3000 dpm of ^{3}H-cholesterol was added to each tube. Tubes were shaken for 30 min. to extract lipids into the organic phase followed by centrifugation for 10 minutes at 1000 x g to separate the organic and aqueous phases. The lower organic phase containing total lipids was removed and placed in a new tube. The organic solution was evaporated under N_2. Resuspend the dry lipid extract in 1 ml. of 93% ethanol containing I M KOH and placed at 70°C for 2.5 hours. After the reaction and cooling, 2 mL of hexane and 2.5 mL of water was

added to each tube followed by rigorous shaking for 10 min. Tubes were centrifuged for 10 mm at 1000 x g and the organic (top) layer containing the non-saponifed lipids was transferred to a new tube followed by evaporation of the organic solvent under N_2. The aqueous phase containing the saponfied lipids was also transferred to a new tube. The non-saponified lipid extract, after drying, was suspended in toluene and an aliquot added to scintillation cocktail followed by radioactive counting. ^{14}C counts representing the incorporation of ^{14}C acetate into non-saponified lipids was corrected by the ^{3}H counts, which represented the extraction efficiency of the procedure as, noted above by the addition of ^{3}H cholesterol. To isolate saponified lipids, 1.5 mL of aqueous phase solution was mixed with 400ul of 1M HCl and then lipids extracted by the addition of 2.5 mL of 2:1 chloroform: methanol, 1.5 ml. of PBS, and 1 mL of water followed by rigorous shaking and isolation of the organic phase. Resuspend the N_2 dried organic phase extraction in toluene, and measure radioactivity using liquid scintillant method. The rate of ^{14}C-acetate incorporation into saponified and non-saponified lipids is reported.

Figure 5 shows the rates of saponified, non-saponified lipid synthesis following treatment with lovastatin and illustrative compounds of the invention. Data are represented as a percent of no compound treatment (Vehicle control). Data are represented as the mean of three measurements +/- one standard deviation. The data indicate that the illustrative compounds of the invention are useful for inhibition of lipid synthesis. In particular, compound A at 30 μM reduced the rates of both saponifiable and non-saponifiable lipid synthesis by at least 97% in the rat hepatocyte cells. Compound B also reduced the rates of both saponified and non-saponified lipids by at least 65% in the rat hepatocyte cells. Accordingly, Compounds A and B, or a pharmaceutically acceptable salt thereof, is useful for inhibiting the synthesis of saponified lipids.

5.6. Cytotoxicity

To evaluate cytotoxicity, monolayer hepatocyte cultures are exposed to increasing concentrations of up to 250 μM Compound A in DMEM for 24 hours. Control cells are exposed to the same media lacking a test compound. All cells are exposed to 0.1% DMSO. The measure of cytotoxicity, release of lactate dehydrogenase (LDH) from the cytosolic compartment of hepatocyte monolayer cultures, reflects damage to the plasma membrane. The assay, is based on the method of Wroblewski and LaDue,1955, *Proc. Soc. Exp. Biol. Med.* 90:210-213; *see also* Ulrich *et al.*, 1995, *Toxicol. Lett.* 82/83:107-115, describing the use of hepatocytes as models for hepatic toxicity), and measures the LDH activity in tissue culture medium and a cell homogenate. Briefly, all the media are removed from plates and

transferred to a separate plate. Following removal of media, attached cells are lysed with a hypotonic Tris/Glycerol/EDTA buffer (0.1 M Tris, 20% glycerol, 1 mM EDTA pH 7.3). Activity of LDH in medium and cells is measured spectrophotometrically by monitoring the rate of pyruvate reduction to lactate, coupled with oxidation of NADH; the rate of absorbance change is measured at 340 nm. Cytotoxicity is expressed as a ratio using the following equation: (LDH in medium / (LDH in medium + LDH in solubilized hepatocytes)) = R.

5.7. Insulin Sensitization Effects

Effects of Compound A on rate of differentiation of 3T3-L1 cells from a "committed pre-adipocyte" to an "adipocyte" phenotype in the absence or presence of insulin can be tested. The differentiation of 3T3-L1 cells to an adipocyte-like phenotype is highly dependent upon insulin. This insulin-dependent changes in cellular morphology and metabolism, including: expression of adipocyte-specific genes, greatly increased levels of glucose uptake and metabolism, induction of GLUT4 (and increased expression of GLUT1) glucose transporters, greatly increased lipid synthesis and deposition of intracellular lipid droplets. In this assay the degree of differentiation is a reflection of the rate of lipid synthesis, as measured through incorporation of ^{14}C-acetate over 2 hours. Thus the ability of a compound to stimulate a submaximal insulin response would suggest an insulin-sensitizing activity (Kletzein *et al.*, 1991, *Molecular Pharm.*41:393-398).

3T3-L1 stem cells are induced to differentiate with dexamethasone, isobutylmethylxanthine and insulin (Green and Kehinde, 1975, *Cell* 5:19-27). Cells are plated in Dulbecco's modified Eagle medium containing 10% calf serum and grown to confluence. Cells are then refreshed with 10% fetal calf serum, and treated with 0.5 mM isobutylmethylxanthine and 250 nM dexamethasone, but no additional insulin, for 48 hours. This treatment induces the differentiation of 3T3-L1 cells into pre-adipocytes. Conversion of preadipocytes to adipocyte phenotype requires the removal of dexamethasone and the presence of insulin, which stimulates differentiation of preadipocytes into adipocytes in a concentration- and time-dependent manner. A maximal insulin effect occurs at about 100 nM insulin, and leads to nearly complete (95-100%) conversion to adipocytes within 4 days.

The preadipocytes are then treated for 4 days with various concentrations of a test compound in 5% fetal calf serum in Dulbecco's modified Eagles medium, with or without a submaximal concentration of insulin (30 nM). Following this four-day treatment, the predipocytes are pulsed with 0.1 mCi ^{14}C-acetate per well for 2 hours. Cell are then washed with phosphate buffered saline, lysed with 0.1 N NaOH, and ^{14}C-acetate incorporation into lipids is determined using phase separation and liquid scintillation counting.

5.8. *In Vivo* Test Results

Compound A was administered daily at a dose of 100 mg/kg to chow-fed male Sprague-Dawley rats for 7 days in the morning by oral gavage in 1.5 percent carboxy-methylcellulose/0.2 percent tween-20 (dosing vehicle). Animals were weighed daily. Animals were allowed free access to rodent chow and water throughout the study period. After the seventh dose, animals were sacrificed in the evening and blood serum was assayed for lipoprotein cholesterol profiles (Figure 2), serum total cholesterol and serum triglycerides (Figure 3). Values for VLDL, LDL and HDL cholesterol, and the ratio of HDL cholesterol to that of VLDL plus LDL cholesterol (Figure 3) were derived from the lipoprotein cholesterol profile (*i.e.*, Figure 2) and the independently determined total cholesterol value (Figure 3). Lipoprotein cholesterol profiles (Figure 2) shows treatment with Compound A results in a 72 percent reduction in VLDL cholesterol ($p<0.0005$), an 88 percent reduction of LDL cholesterol ($p<0.0001$), and a non-significant 3 percent increase of HDL cholesterol when compared to animals treated with the dosing vehicle alone. Compound A treatment also reduces total serum cholesterol by 30 percent ($p<0.0005$) and serum triglycerides by 64 percent ($p<0.0005$) (Figure 2). The change in total cholesterol as reflected by the reduction in VLDL plus LDL cholesterol and the slight elevation in HDL cholesterol resulted in a HDL to VLDL plus LDL cholesterol ratio from 1.7 ± 0.1 (control) to 17.0 ± 6.9 (Compound A treated); a 9.9 fold improvement in the ratio (Figure 2). Compared to pretreatment body weights, Compound A caused a reduction in body weight gain (30.4 ± 0.6 percent weight gain) compared to the control group (34.3 ± 0.7 percent weight gain) after seven days.

Dosing vehicle or Compound A (93 mg/kg) was administered to 9-10 week old female obese Zucker rats (i.e. the fa/fa or leptin receptor deficient rat) daily for 14 days in the morning by oral gavage in 1.5 percent carboxymethylcellulose/0.2 percent tween-20. Tail vein blood for glucose determinations (without anesthesia) and orbital blood samples for serum (with anestehesia for all other determinations) were obtained following a 6 hour fast prior to the initial dose and after one and two weeks of dosing.

Blood serum were assayed for insulin, non-esterified fatty acids, ß-hydroxy butyrate, total cholesterol, and triglycerides (Figure 5). Glucose was determined in whole blood (Figure 5). Blood serum was also used to produce lipoprotein cholesterol profiles (Figure 4), and used to determine VLDL plus LDL cholesterol combined (also referred to as apoB containing lipoprotein cholesterol or non-HDL cholesterol), HDL cholesterol, and the ratio of HDL cholesterol to that of VLDL plus LDL cholesterol (Figure 5). In addition, the effect of Compound A on weight gain after 14 days and the liver to body weight ratio at sacrifice are shown in Figure 5.

In the Zucker rat. Compound A increased total serum cholesterol by 33, and 79 percent after one and two weeks of treatment, respectively. Vehicle treatment resulted in only a –10 and 10 change of total serum cholesterol after one and two weeks of treatment, respectively (Figure 5). Serum triglycerides were reduced by 60 and 62 percent with ESP31015 treatment after one and two weeks of treatment (Figure 5).

Lipoprotein cholesterol profiles shows treatment with Compound A resulted in a marked alteration in the distribution of cholesterol among lipoproteins (Figure 4). In particular, Compound A caused a marked elevation in HDL cholesterol after one week of treatment, which was further elevated after two weeks of treatment. Using the serum total cholesterol values (Figure 5) and the lipoprotein cholesterol distribution (Figure 4), the amount of cholesterol associated with non-HDL (i.e. VLDL plus LDL cholesterol) and HDL cholesterol were determined (Figure 5). Compound A decreased non-HDL cholesterol by 58 and 27 percent, and markedly increased HDL cholesterol 2.3-fold and 3.2-fold after one and two weeks treatment, respectively. When these data are expressed as a ratio of HDL/non-HDL cholesterol, it can be clearly seen Compound A markedly improves the ratio from 0.83 (pretreatment) to 2.97 and 3.45 after one-week and two-weeks of treatment, respectively.

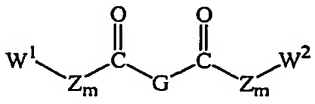
Impaired glucose tolerance is the metabolic symptom beginning at about 8-12 weeks of age in obese female Zucker rats and therefore the animals are able to maintain normal glucose levels at the expense of elevated insulin levels. As shown in Figure 5, pretreatment and posttreatment blood glucose levels were similar after one and two weeks of Compound A treatment. An indication of an improved diabetic state is the reduction of non-esterified fatty acids from 2.51 to 0.77 mmol/L after two weeks of Compound A coupled to an elevation in ß-hydroxy butyrate. These data may reflect an enhanced hepatic ß-oxidation of excess fatty acids resulting from the reduction of serum non-esterified fatty acids and triglycerides (Figure 5). Compound A treatment did not induce a hypoglycemic state.

The present invention is not to be limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few aspects of the invention and any embodiments which are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the appended claims.

THE CLAIMS

What is claimed is:

1. A compound of a formula **I**:



I

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, stereoisomer, geometric isomer or mixtures thereof wherein:

(a) each occurrence of Z is independently CH_2, CH=CH, or phenyl, where each occurrence of m is independently an integer ranging from 1 to 9, but when Z is phenyl then its associated m is 1;

(b) G is $(CH_2)_x$, $CH_2CH=CHCH_2$, $CH=CH$, CH_2–phenyl–CH_2, or phenyl, where x is 2, 3, or 4;

(c) W^1 and W^2 are independently L, V, $C(R^1)(R^2)$–$(CH_2)_c$–$C(R^3)(R^4)$–$(CH_2)_n$–Y, or $C(R^1)(R^2)$–$(CH_2)_c$–V where c is 1 or 2 and n is an independent integer ranging from 0 to 4;

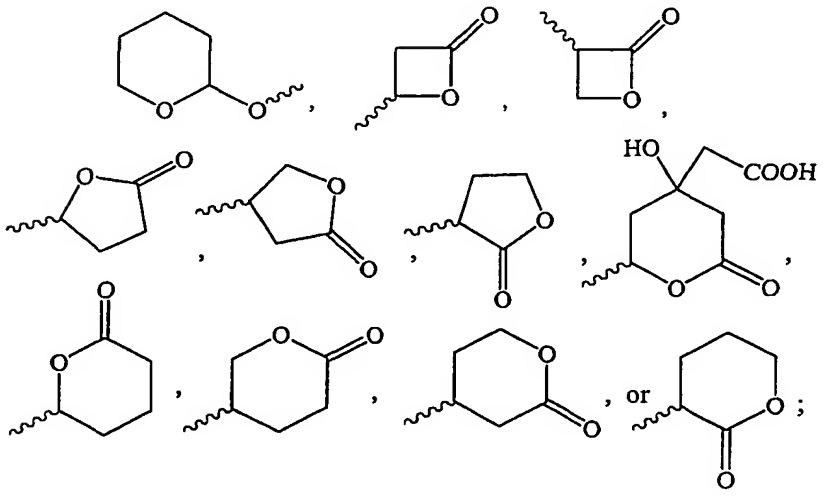
(d) each occurrence of R^1 or R^2 is independently $(C_1$–$C_6)$alkyl, $(C_2$–$C_6)$alkenyl, $(C_2$–$C_6)$alkynyl, phenyl, or benzyl or when one or both of W^1 and W^2 is $C(R^1)(R^2)$–$(CH_2)_c$–$C(R^3)(R^4)$–$(CH_2)_n$–Y, then R^1 and R^2 can both be H to form a methylene group;

(e) R^3 is H, $(C_1$–$C_6)$alkyl, $(C_2$–$C_6)$alkenyl, $(C_2$–$C_6)$alkynyl, $(C_1$–$C_6)$alkoxy, phenyl, benzyl, Cl, Br, CN, NO_2, or CF_3;

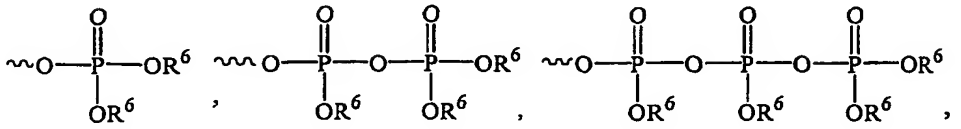
(f) R^4 is OH, $(C_1$–$C_6)$alkyl, $(C_2$–$C_6)$alkenyl, $(C_2$–$C_6)$alkynyl, $(C_1$–$C_6)$alkoxy, phenyl, benzyl, Cl, Br, CN, NO_2, or CF_3;

(g) L is $C(R^1)(R^2)$–$(CH_2)_n$ –Y where n is an independent integer ranging from 0 to 4;

(h) V is



(i) each occurrence of Y is independently OH, COOH, CHO, $COOR^5$, SO_3H,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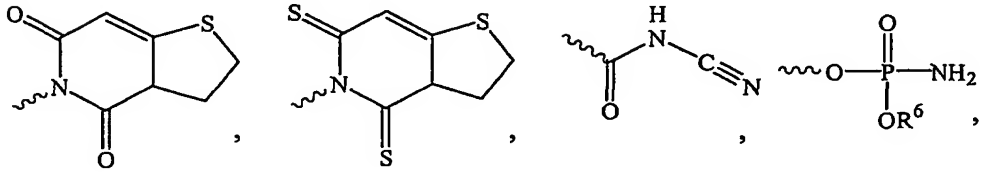
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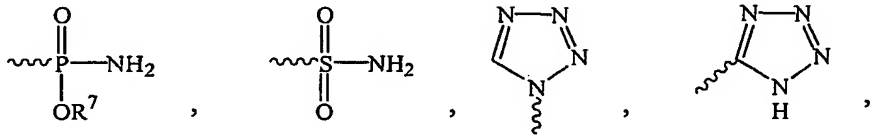
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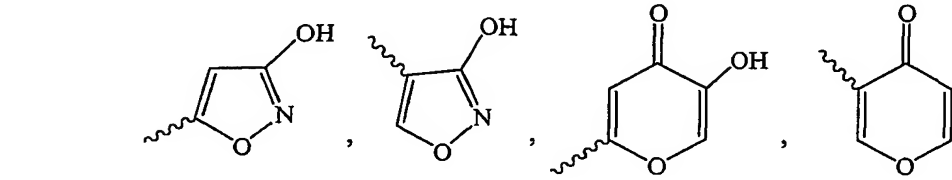
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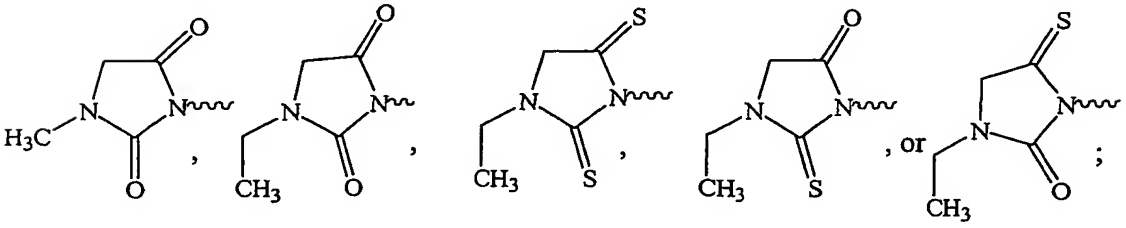

;

where

(i) R^5 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, $(C_1–C_6)$alkoxy, or phenyl groups,

(ii) each occurrence of R^6 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl and is unsubstituted or substituted with one or two halo, OH, $(C_1–C_6)$ alkoxy, or phenyl groups, and

(iii) each occurrence of R^7 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl;

provided that:

(i) if G is $(CH_2)_x$, x is 4, each occurrence of Z is CH_2, each occurrence of m is 4, and W^1 is $-CH(CH_3)CO_2H$, then W^2 is not the same as W^1;

(ii) if G is CH_2-phenyl-CH_2, each occurrence of Z is CH_2, each occurrence of m is 2, and W^1 is $-C(CH_3)_2CH(CO_2CH_2CH_3)_2$, then W^2 is not the same as W^1;

(iii) if G is CH_2-phenyl-CH_2, each occurrence of Z is CH_2, each occurrence of m is 2, and W^1 is $-C(CH_3)_2CH_2(CO_2CH_2CH_3)$, then W^2 is not the same as W^1;

(iv) if G is CH_2-phenyl-CH_2, each occurrence of Z is CH_2, each occurrence of m is 1, and W^1 is $-COCH_2C(CH_3)_2CH_2CO_2H$, then W^2 is not the same as W^1;

(v) if G is $(CH_2)_x$, x is 4, each occurrence of Z is CH_2, each occurrence of m is 2, and W^1 is $-C(phenyl)_2CH_2CO_2H$, then W^2 is not the same as W^1;

(vi) if G is CH=CH, each occurrence of Z is CH_2, each occurrence of m is 1, and W^1 is $-C(CH_3)_2CH_2(CO_2H)$, then W^2 is not the same as W^1; and

(vii) if G is phenyl, each occurrence of Z is CH_2, each occurrence of m is 1, and W^1 is $-C(phenyl)_2CO_2H$, then W^2 is not the same as W^1.

2. The compound of claim 1, wherein:

(a) W^1 and W^2 are independently L, V, or $C(R^1)(R^2)–(CH_2)_c–V$ where c is 1 or 2; and

(b) R^1 or R^2 are independently $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl.

3. The compound of claim 1, wherein W^1 is L.

4. The compound of claim 1, wherein W^1 is V.

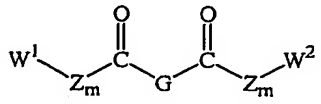
5. The compound of claim 1, wherein W^1 is $C(R^1)(R^2)$–$(CH_2)_c$–$C(R^3)(R^4)$–$(CH_2)_n$-Y.

6. The compound of claim 1, wherein W^1 is $C(R^1)(R^2)$–$(CH_2)_c$–V.

7. The compound of claim 1, wherein W^1 and W^2 are independent L groups.

8. The compound of claim 7, wherein each occurrence of Y is independently OH, $COOR^5$, or COOH.

9. A compound of the formula **Ia**:



Ia

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, stereoisomer, geometric isomer or mixtures thereof wherein:

(a) each occurrence of Z is independently CH_2 or CH=CH, where each occurrence of m is independently an integer ranging from 1 to 9;

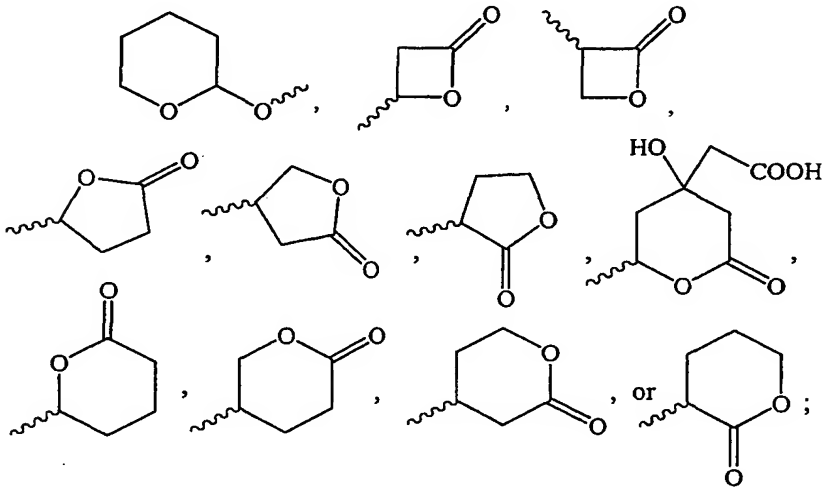
(b) G is $(CH_2)_x$, CH_2CH=$CHCH_2$, or CH=CH, where x is 2, 3, or 4;

(c) W^1 and W^2 are independently L, V, or $C(R^1)(R^2)$–$(CH_2)_c$–V where c is 1 or 2;

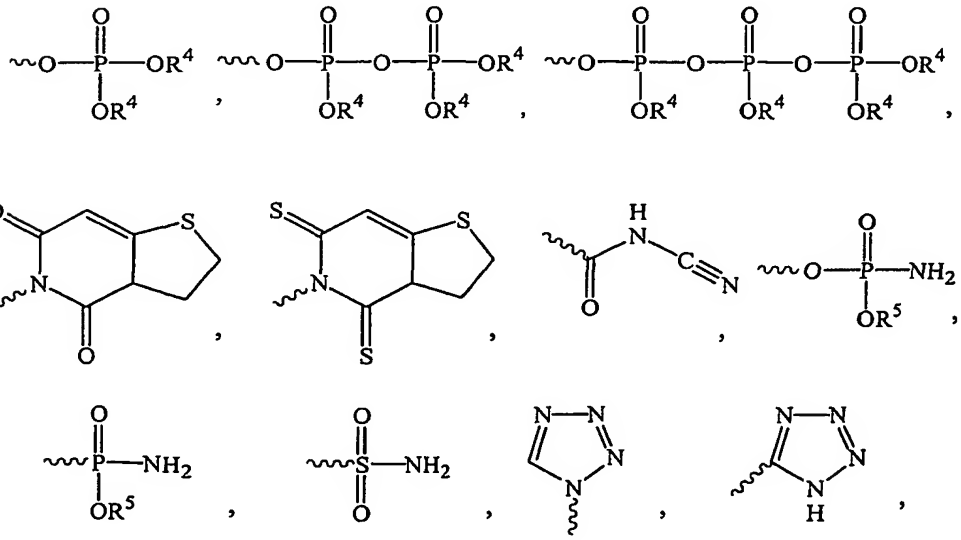
(d) each occurrence of R^1 or R^2 is independently $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl;

(e) L is $C(R^1)(R^2)–(CH_2)_n–Y$ where n is an independent integer ranging from 0 to 4;;

(f) V is

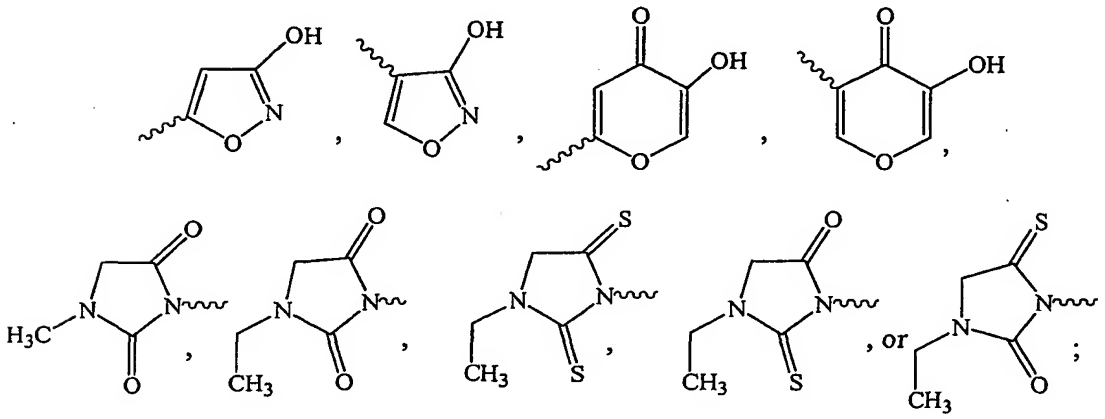


(g) each occurrence of Y is independently OH, COOH, CHO, $COOR^3$, SO_3H,



where:

(i) R^3 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, $(C_1–C_6)$alkoxy, or phenyl groups,



(ii) each occurrence of R^4 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl and is unsubstituted or substituted with one or two halo, OH, $(C_1–C_6)$alkoxy, or phenyl groups, and

(iii) each occurrence of R^5 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl;

provided that:

(i) if x is 4, each occurrence of Z is CH_2, each occurrence of m is 4, and W^1 is $-CH(CH_3)CO_2H$, then W^2 is not the same as W^1; and

(ii) if x is 4, each occurrence of Z is CH_2, each occurrence of m is 2, and W^1 is $-C(phenyl)_2CH_2CO_2H$, then W^2 is not the same as W^1.

10. The compound of claim 9, wherein W^1 is L.

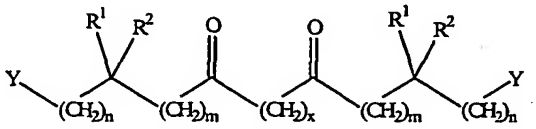
11. The compound of claim 9, wherein W^1 is V.

12. The compound of claim 9, wherein W^1 is $C(R^1)(R^2)–(CH_2)_c–V$.

13. The compound of claim 9, wherein W^1 and W^2 are independent L groups.

14. The compound of claim 13, wherein each occurrence of Y is independently OH, $COOR^3$, or COOH.

15. A compound of the formula **Ib**



Ib

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, stereoisomer, geometric isomer or mixtures thereof wherein:

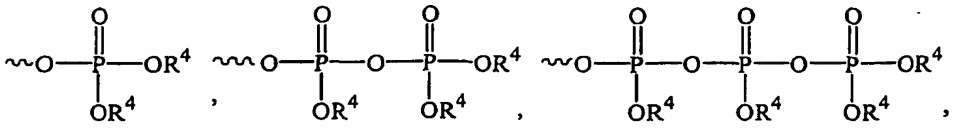
(a) each occurrence of m is independently an integer ranging from 1 to 9;

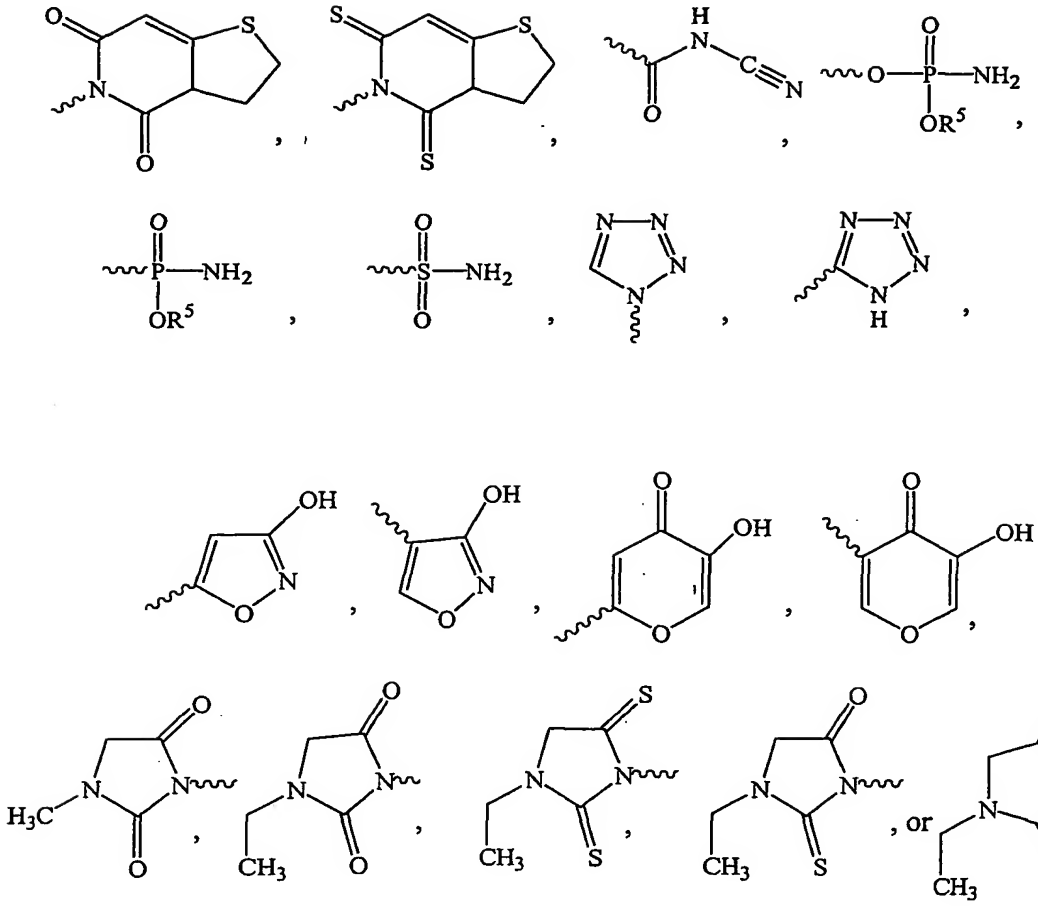
(b) x is 2, 3, or 4;

(c) each occurrence of n is independently an integer ranging from 0 to 4;

(d) each occurrence of R^1 or R^2 is independently $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl; and

(e) each occurrence of Y is independently OH, COOH, CHO, $COOR^3$, SO_3H,





where:

(i) R^3 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, $(C_1–C_6)$alkoxy, or phenyl groups,

(ii) each occurrence of R^4 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl and is unsubstituted or substituted with one or two halo, OH, $C_1–C_6$ alkoxy, or phenyl groups; and

(iii) each occurrence of R^5 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl;

provided that:

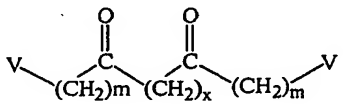
(i) if x is 4 each occurrence of m is 4, and W^1 is $-CH(CH_3)CO_2H$, then W^2 is not the same as W^1; and

(ii) if x is 4 occurrence of m is 2, and W^1 is $-C(phenyl)_2CH_2CO_2H$, then W^2 is not the same as W^1.

16. The compound of claim 15, wherein each occurrence of Y is independently OH, $COOR^3$, or COOH.

17. The compound of claim 16, wherein each R^1 or R^2 is the same or different $(C_1–C_6)$alkyl group.

18. A compound of the formula **Ic**



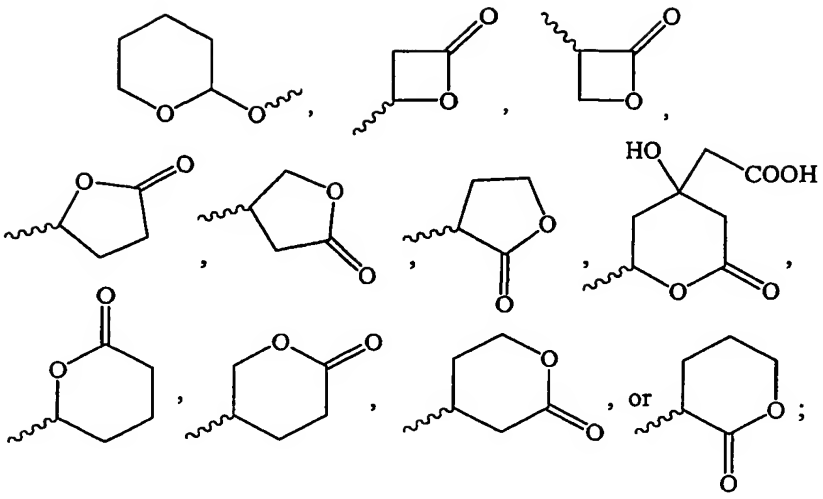
Ic

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, stereoisomer, geometric isomer or mixtures thereof wherein:

(a) each occurrence of m is an independent integer ranging from 1 to 9;

(b) x is 2, 3, or 4;

(c) V is



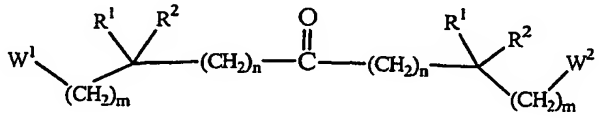
provided that:

(i) if x is 4 each occurrence of m is 4, and W^1 is $-CH(CH_3)CO_2H$, then W^2 is not the same as W^1; and

(ii) if x is 4 each occurrence of m is 2, and W^1 is $-C(phenyl)_2CH_2CO_2H$, then W^2 is not the same as W^1.

19. A compound according to claim 1, having the formula 5-[2-(5-hydroxy-4,4-dimethyl-pentyloxy)-ethoxy]-2,2-dimethyl-pentan-1-ol or 4-[3-(3,3-Dimethyl-4-oxo-butoxy)-propoxy]-2,2-dimethyl-butyric acid.

20. A compound of the formula **II**:



II

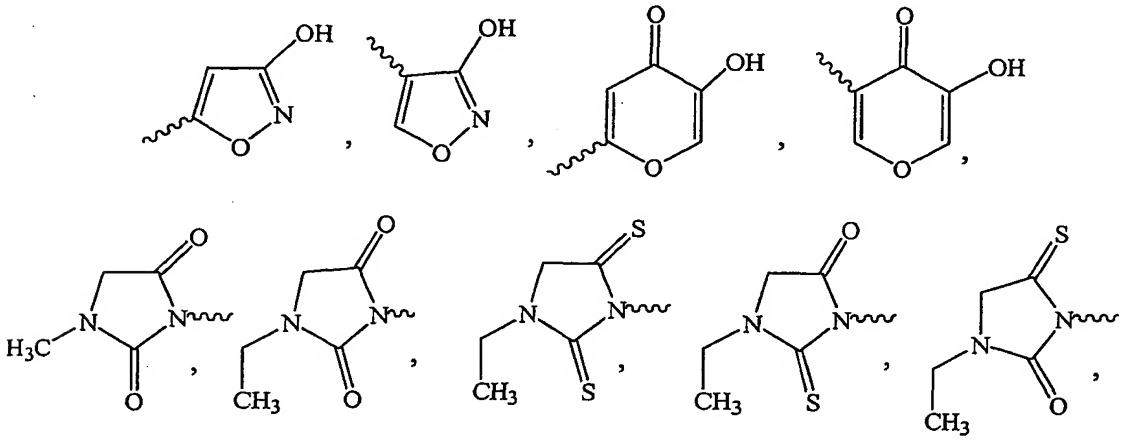
or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, stereoisomer, geometric isomer or mixtures thereof wherein:

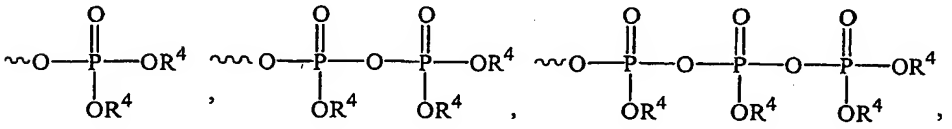
(a) R^1 and R^2 are independently $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl; or R^1, R^2, and the carbon to which they are both attached are taken together to form a $(C_3–C_7)$cycloalkyl group;

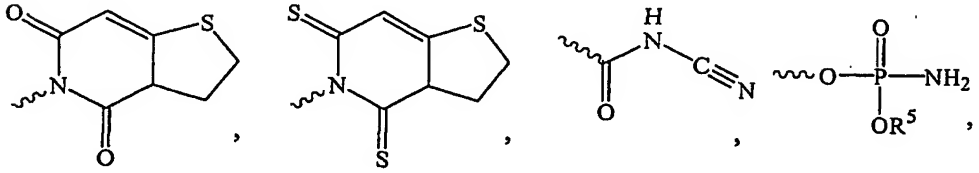
(b) n is an integer ranging from 1 to 5;

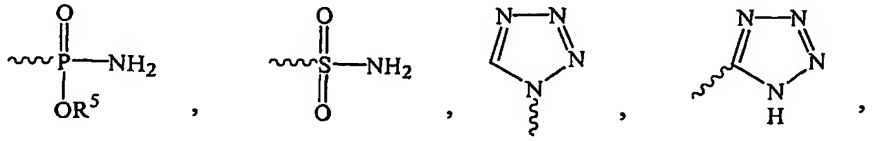
(c) each occurrence of m is independently an integer ranging from 0 to 4;

(d) each occurrance of W^1 and W^2 is independently CH_2OH, COOH, CHO, $OC(O)R^3$, $C(O)OR^3$, SO_3H,





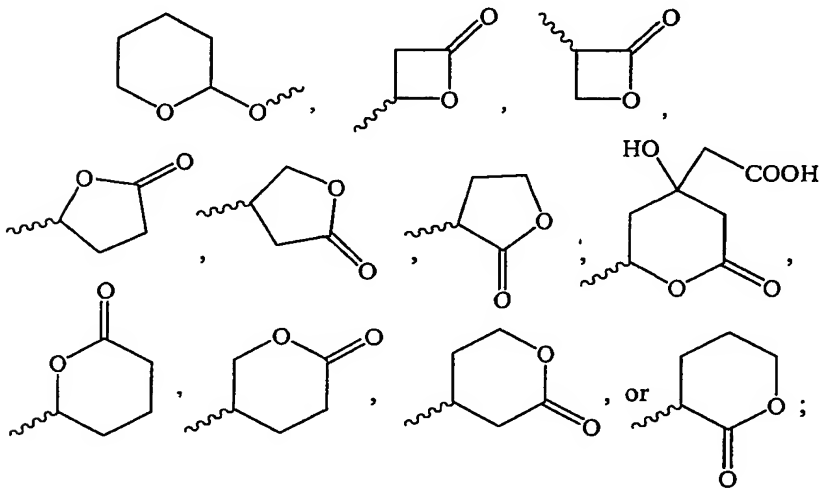




where:

(i) R^3 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, $(C_1–C_6)$alkoxy, or phenyl groups,

(ii) each occurrence of R^4 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl and is unsubstituted or substituted

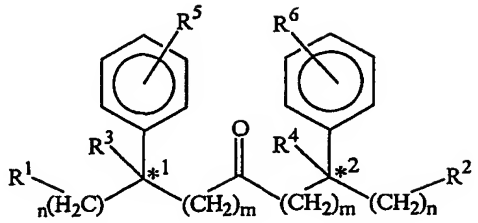


with one or two halo, OH, $C_1–C_6$ alkoxy, or phenyl groups,

(iii) each occurrence of R^5 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl; and

(iv) each occurrence of n is independently an integer ranging from 0 to 4.

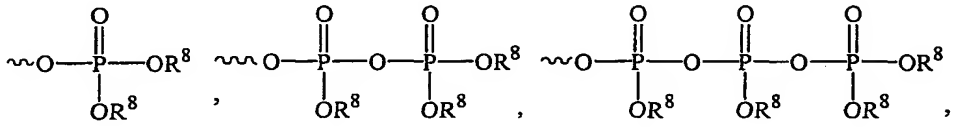
21. A compound of the formula **IIa**:

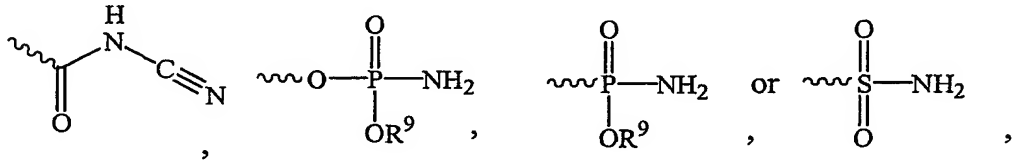


IIa

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, stereoisomer, geometric isomer or mixtures thereof wherein:

(a) R^1 and R^2 are OH, COOH, CHO, $COOR^7$, SO_3H,





where:

(i) R^7 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, $(C_1–C_6)$alkoxy, or phenyl groups,

(ii) each occurrence of R^8 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl and is unsubstituted or substituted with one or two halo, OH, $C_1–C_6$ alkoxy, or phenyl groups,

(iii) each occurrence of R^9 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl;

(b) R^3 and R^4 are $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl;

(c) R^5 and R^6 are hydrogen, halogen, $(C_1–C_4)$alkyl, $(C_1–C_4)$alkoxy, (C_6)aryloxy, CN, or NO_2, $N(R^5)_2$ where R^5 is H, $(C_1–C_4)$alkyl, phenyl, or benzyl;

(d) each occurrence of m is independently an integer ranging from 1 to 5;

(e) each occurrence of n is independently an integer ranging from 0 to 4; and

(f) C^{*1} and C^{*2} each represent independent chiral-carbon centers, wherein each center may independently be R or S.

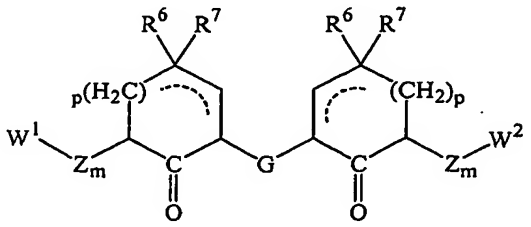
22. The compound of claim 21 wherein C^{*1} is a chiral-carbon center of the stereochemical configuration R or substantially R.

23. The compound of claim 21 wherein C^{*1} is a chiral-center of the stereochemical configuration S or substantially S.

24. The compound of claim 21 wherein C^{*2} is a chiral-carbon center of the stereochemical configuration R or substantially R.

25. The compound of claim 21 wherein C^{*2} is a chiral-center of the stereochemical configuration S or substantially S.

26. A compound of the formula **III**:



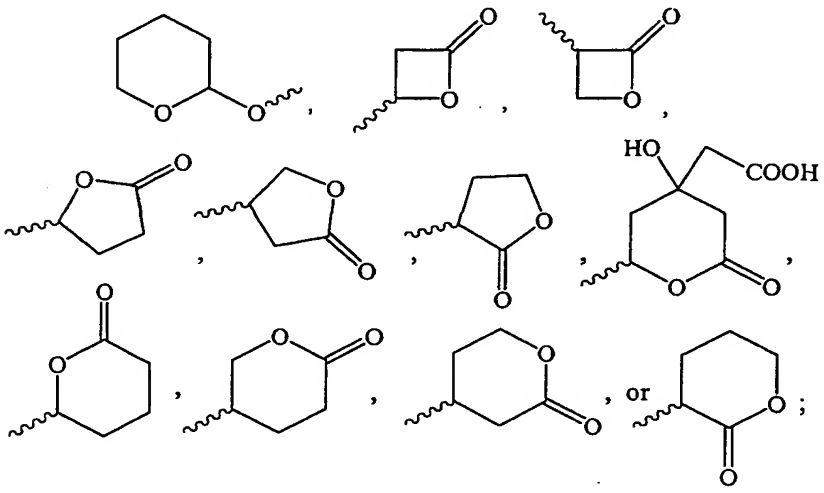
III

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, stereoisomer, geometric isomer or mixtures thereof wherein:

(a) each occurrence of Z is independently CH_2, CH=CH, or phenyl, where each occurrence of m is independently an integer ranging from 1 to 5, but when Z is phenyl then its associated m is 1;

(b) G is $(CH_2)_x$, $CH_2CH=CHCH_2$, CH=CH, CH_2–phenyl–CH_2, or phenyl, where x is an integer ranging from 1 to 4;

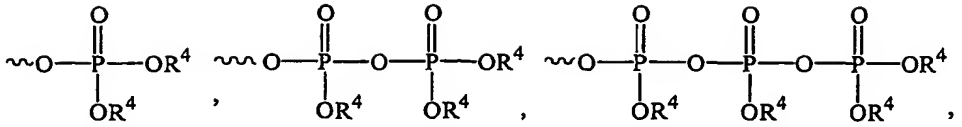
(c) W^1 and W^2 are independently $C(R^1)(R^2)$–$(CH_2)_n$–Y where n is an independent integer ranging from 0 to 4;

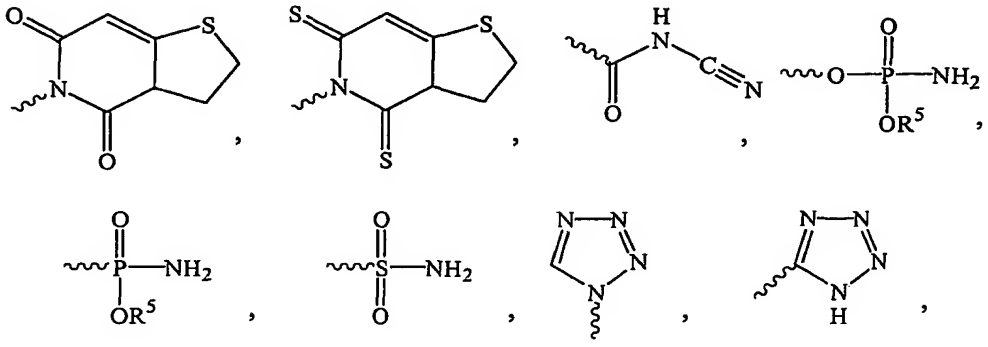


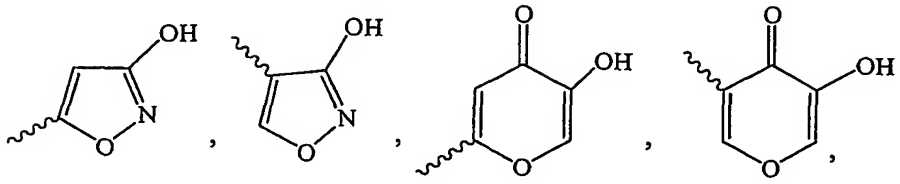
(d) each occurrence of R^1 or R^2 is independently $(C_1$–$C_6)$alkyl, $(C_2$–$C_6)$alkenyl, $(C_2$–$C_6)$alkynyl, phenyl, or benzyl, or where R^1 and R^2 are both hydrogen;

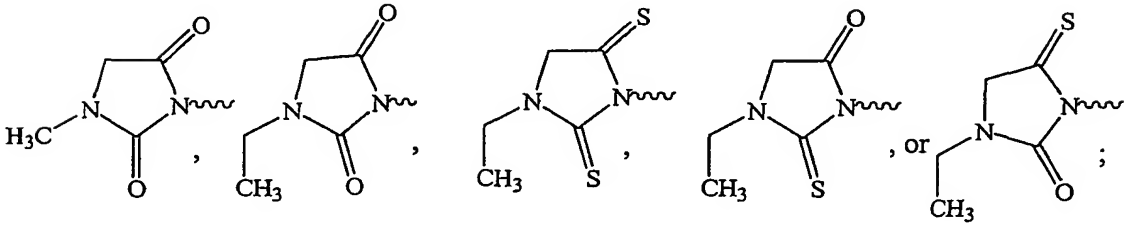
(e) each occurrence of R^6 and R^7 are independently H, $(C_1$-$C_6)$alkyl, or where R^6 and R^7 are taken together to form a carbonyl group;

(f) each occurrence of Y is independently OH, COOH, CHO, $COOR^3$, SO_3H,









where:

(i) R^3 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, $(C_1–C_6)$alkoxy, or phenyl groups,

(ii) each occurrence of R^4 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl and is unsubstituted or substituted with one or two halo, OH, $C_1–C_6$ alkoxy, or phenyl groups,

(iii) each occurrence of R^5 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl, and

(g) each occurrence of p is independently 0 or 1 where the broken line represents an optional presence of one or more additional carbon-carbon bonds that when present complete one or more carbon-carbon double bonds.

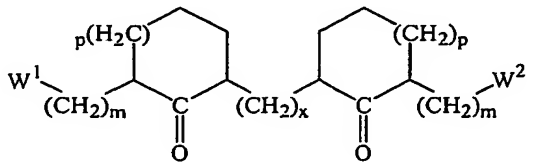
27. The compound of claim 26, wherein W^1 and W^2 are independent $C(R^1)(R^2)–(CH_2)_n–Y$ groups, where n is an independent integer ranging from 0 to 4, and each occurrence of Y is independently OH, $COOR^4$, or COOH.

28. The compound of claim 26, wherein p is 0.

29. The compound of claim 26, wherein p is 1.

30. The compound of claim 26 wherein each occurrence of R_6 and R_7 is hydrogen;

31. A compound of the formula **IIIa**:



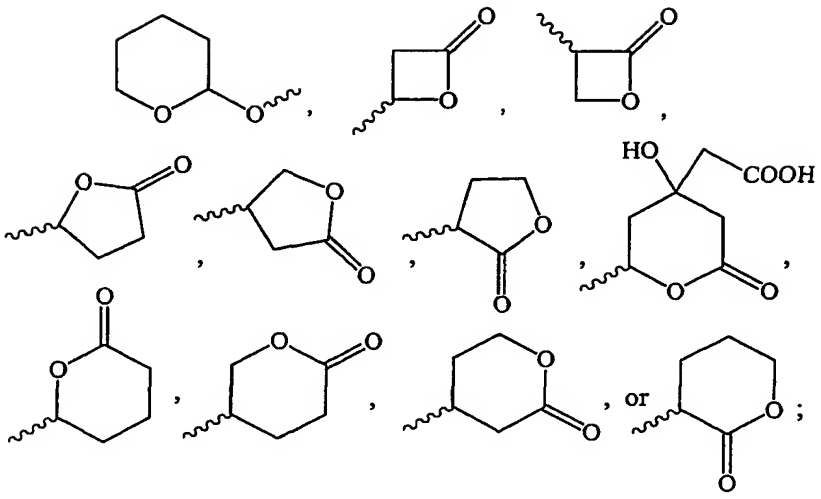
IIIa

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, stereoisomer, geometric isomer or mixtures thereof wherein:

(a) each occurrence of m is independently an integer ranging from 1 to 5;

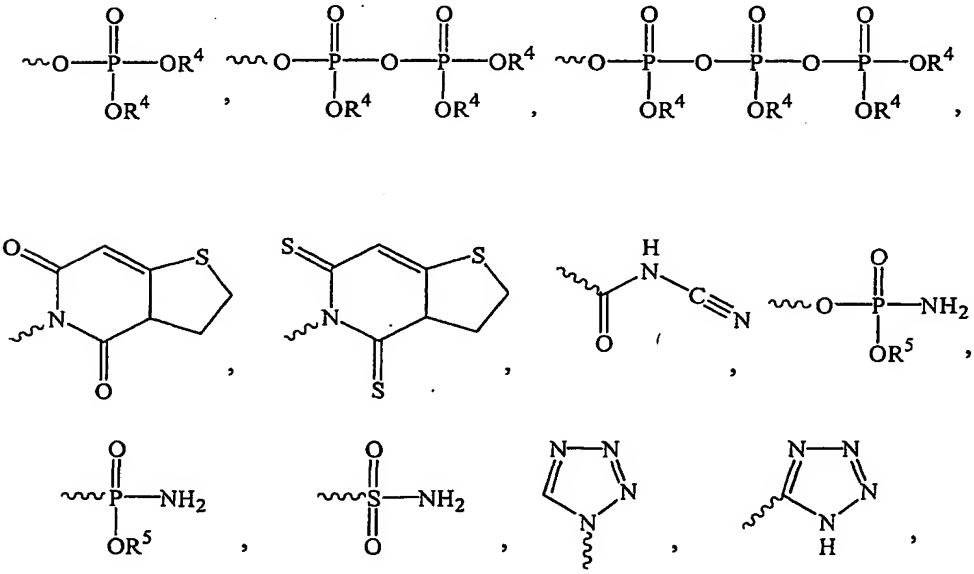
(b) x is an integer ranging from 1 to 4;

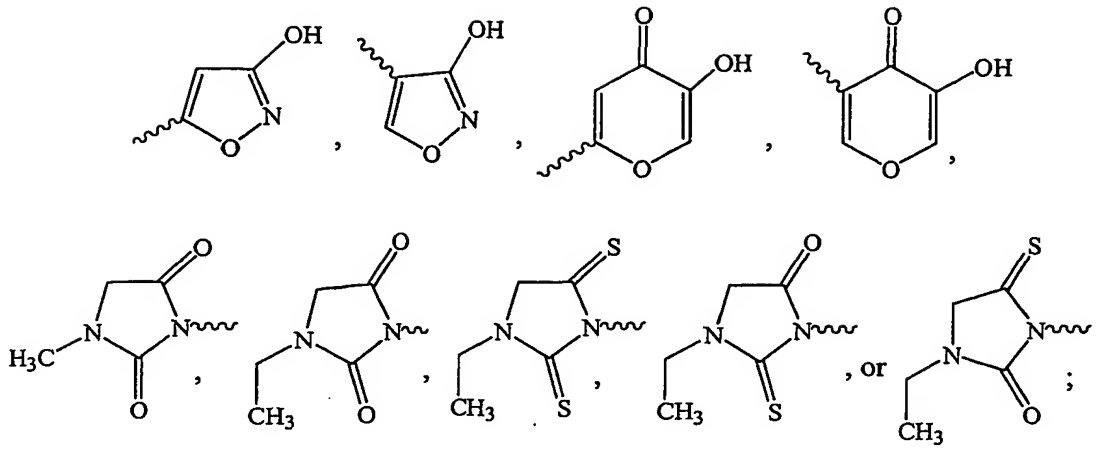
(c) W^1 and W^2 are independently $C(R^1)(R^2)–(CH_2)_n–Y$ where n is an integer from 0 to 4,



(d) each occurrence of R^1 or R^2 is independently $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl;

(e) each occurrence of Y is independently OH, COOH, CHO, $COOR^3$, SO_3H,





where

(i) R^3 is $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, $(C_1–C_6)$alkoxy, or phenyl groups,

(ii) each occurrence of R^4 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl and is unsubstituted or substituted with one or two halo, OH, $C_1–C_6$ alkoxy, or phenyl groups,

(iii) each occurrence of R^5 is independently H, $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, or $(C_2–C_6)$alkynyl, and

(f) each occurrence of p is independently 0 or 1.

32. The compound of claim 31, wherein W^1 and W^2 are independent $C(R^1)(R^2)–(CH_2)–Y$ groups, and each occurrence of Y is independently $-(CH_2)_nOH$, $-(CH_2)_nCOOR^3$, or $-(CH_2)_nCOOH$.

33. The compound of claim 31, wherein p is 0.

34. The compound of claim 31, wherein p is 1.

35. A compound having the formula:

I-1 5-Hydroxy-1-[4-(5-hydroxy-5-methyl-2-oxo-hexyl)-phenyl]-5-methyl-hexan-2-one;

I-2 6-Hydroxy-1-[4-(6-hydroxy-5,5-dimethyl-2-oxo-hexyl)-phenyl]-5,5-dimethyl-hexan-2-one;

I-3 6-[4-(5-Carboxy-5-methyl-2-oxo-hexyl)-phenyl]-2,2-dimethyl-5-oxo-hexanoic acid;

I-4 6-[4-(5,5-Dimethyl-2,6-dioxo-hexyl)-phenyl]-2,2-dimethyl-5-oxo-hexanal;

I-5 6-[4-(5-Methoxycarbonyl-5-methyl-2-oxo-hexyl)-phenyl]-2,2-dimethyl-5-oxo-hexanoic acid methyl ester;

I-6 2,2-Dimethyl-6-[4-(5-methyl-2-oxo-5-phenoxycarbonyl-hexyl)-phenyl]-5-oxo-hexanoic acid phenyl ester;

I-7 6-[4-(5-Benzyloxycarbonyl-5-methyl-2-oxo-hexyl)-phenyl]-2,2-dimethyl-5-oxo-hexanoic acid benzyl ester;

I-8 2-Methyl-6-[4-(5-methyl-2-oxo-5-sulfo-hexyl)-phenyl]-5-oxo-hexane-2-sulfonic acid;

I-9 Phosphoric acid mono-{1,1-dimethyl-5-[4-(5-methyl-2-oxo-5-phosphonooxy-hexyl)-phenyl]-4-oxo-pentyl} ester;

I-10 4-Hydroxy-1-[4-(4-hydroxy-4-methyl-pentanoyl)-phenyl]-4-methyl-pentan-1-one;

I-11 5-Hydroxy-1-[4-(5-hydroxy-4,4-dimethyl-pentanoyl)-phenyl]-4,4-dimethyl-pentan-1-one;

I-12 5-[4-(4-Carboxy-4-methyl-pentanoyl)-phenyl]-2,2-dimethyl-5-oxo-pentanoic acid;

I-13 5-[4-(4,4-Dimethyl-5-oxo-pentanoyl)-phenyl]-2,2-dimethyl-5-oxo-pentanal;

I-14 5-[4-(4-Methoxycarbonyl-4-methyl-pentanoyl)-phenyl]-2,2-dimethyl-5-oxo-pentanoic acid methyl ester;

I-15 2,2-Dimethyl-6-[4-(5-methyl-2-oxo-5-phenoxycarbonyl-hexyl)-phenyl]-5-oxo-hexanoic acid phenyl ester;

I-16 5-[4-(4-Benzyloxycarbonyl-4-methyl-pentanoyl)-phenyl]-2,2-dimethyl-5-oxo-pentanoic acid benzyl ester;

I-17 2-Methyl-5-[4-(4-methyl-4-sulfo-pentanoyl)-phenyl]-5-oxo-pentane-2-sulfonic acid;

I-18 Phosphoric acid mono-{1,1-dimethyl-4-[4-(4-methyl-4-phosphonooxy-pentanoyl)-phenyl]-4-oxo-butyl} ester;

Ib-1 2,12-Dihydroxy-2,12-dimethyl-tridecane-5,9-dione;

Ib-2 1,13-Dihydroxy-2,2,12,12-tetramethyl-tridecane-5,9-dione;

Ib-3 2,2,12,12-Tetramethyl-5,9-dioxo-tridecanedioic acid;

Ib-4 2,2,12,12-Tetramethyl-5,9-dioxo-tridecanedial;

Ib-5 2,2,12,12-Tetramethyl-5,9-dioxo-tridecanedioic acid dimethyl ester;

Ib-6 2,2,12,12-Tetramethyl-5,9-dioxo-tridecanedioic acid diphenyl ester;

Ib-7 2,2,12,12-Tetramethyl-5,9-dioxo-tridecanedioic acid dibenzyl ester;

Ib-8 2,12-Dimethyl-5,9-dioxo-tridecane-2,12-disulfonic acid;

Ib-9 Phosphoric acid mono-(1,1,11-trimethyl-4,8-dioxo-11-phosphonooxy-dodecyl) ester;

Ib-10 2,12-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,12-dimethyl-tridecane-5,9-dione;

Ib-11 2,12-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,12-dimethyl-tridecane-5,9-dione;

Ib-12 2,2,12,12-Tetramethyl-5,9-dioxo-tridecanedioic acid dicyanimide

Ib-13 Phosphoramidic acid mono-[11-(amino-hydroxy-phosphoryloxy)-1,1,11-trimethyl-4,8-dioxo-dodecyl] ester;

Ib-14 2,12-Dimethyl-2,12-bis-(amino-hydroxy-phosphoryloxy)-tridecane-5,9-dione;

Ib-15 2,12-Dimethyl-2,12-bis-tetrazol-1-yl-tridecane-5,9-dione;

Ib-16 2,12-Dimethyl-2,12-bis-(1*H*-tetrazol-5-yl)-tridecane-5,9-dione;

Ib-17 2,12-Bis-(3-hydroxy-isoxazol-5-yl)-2,12-dimethyl-tridecane-5,9-dione;

Ib-18 2,12-Bis-(3-hydroxy-isoxazol-4-yl)-2,12-dimethyl-tridecane-5,9-dione;

Ib-19 2,12-Bis-(5-hydroxy-4-oxo-4*H*-pyran-3-yl)-2,12-dimethyl-tridecane-5,9-dione;

Ib-20 2,12-Bis-(5-hydroxy-4-oxo-4*H*-pyran-2-yl)-2,12-dimethyl-tridecane-5,9-dione;

Ib-21 1-Ethyl-3-[11-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-1,1,11-trimethyl-4,8-dioxo-dodecyl]-imidazolidine-2,4-dione;

Ib-22 2,12-Bis-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-2,12-dimethyl-tridecane-5,9-dione;

Ib-23 2,12-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-2,12-dimethyl-tridecane-5,9-dione;

Ib-24 2,12-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-2,12-dimethyl-tridecane-5,9-dione;

Ib-25 1,15-Dihydroxy-3,3,13,13-tetramethyl-pentadecane-6,10-dione;

Ib-26 3,3,13,13-Tetramethyl-6,10-dioxo-pentadecanedioic acid;

Ib-27 3,3,13,13-Tetramethyl-6,10-dioxo-pentadecanedial;

Ib-28 3,3,13,13-Tetramethyl-6,10-dioxo-pentadecanedioic acid dimethyl ester;

Ib-29 2,2,12,12-Tetramethyl-5,9-dioxo-tetradecanedioic acid diphenyl ester;

Ib-30 3,3,13,13-Tetramethyl-6,10,14-trioxo-16-phenyl-hexadecanoic acid benzyl ester;

Ib-31 2,2,12,12-Tetramethyl-5,9-dioxo-tridecane-1,13-disulfonic acid;

Ib-32 Phosphoric acid mono-(2,2,12,12-tetramethyl-5,9-dioxo-13-phosphonooxy-tridecyl) ester;

Ib-33 1,13-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione;

Ib-34 1,13-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione;

Ib-35 3,3,13,13-Tetramethyl-6,10-dioxo-pentadecanedioic acid dicyanimide

Ib-36 Phosphoramidic acid mono-[13-(amino-hydroxy-phosphoryloxy)-2,2,12,12-tetramethyl-6,9-dioxo-tridecyl] ester;

Ib-37 Phosphoramidic acid mono-[11-(amino-hydroxy-phosphoryloxy)-1,1,11- trimethyl- 4 ,8- dioxo-dodecyl] ester;

Ib-38 2,2,12,12-Tetramethyl-1,13-bis-tetrazol-1-yl-tridecane-5,9-dione;

Ib-39 1,13-Bis-(3-hydroxy-isoxazol-5-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione;

Ib-40 1,13-Bis-(3-hydroxy-isoxazol-5-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione;

Ib-41 1,13-Bis-(3-hydroxy-isoxazol-4-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione;

Ib-42 1-(5-Hydroxy-4-oxo-4*H*-pyran-3-yl)-13-(5-hydroxy-4-oxo-4*H*-pyran-2-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione;

Ib-43 1,13-Bis-(5-hydroxy-4-oxo-4*H*-pyran-2-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione;

Ib-44 1,13-Bis-(5-hydroxy-4-oxo-4*H*-pyran-3-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione;

Ib-45 1-Ethyl-3-[13-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-2,2,12,12-tetramethyl-5,9-dioxo-tridecyl]-imidazolidine-2,4-dione;

Ib-46 1,13-Bis-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione;

Ib-47 1,13-Bis-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione;

Ib-48 1,13-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione;

Ib-49 1,13-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-2,2,12,12-tetramethyl-tridecane-5,9-dione;

Ib-50 2,11-Dihydroxy-2,11-dimethyl-dodecane-5,8-dione;

Ib-51 1,12-Dihydroxy-2,2,11,11-tetramethyl-dodecane-5,8-dione;

Ib-52 2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid;

Ib-53 2,11-Dimethyl-5,8-dioxo-dodecane-2,11-disulfonic acid;

Ib-54 2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedial;

Ib-55 2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid dimethyl ester;

Ib-56 2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid diphenyl ester;

Ib-57 2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid dibenzyl ester;

Ib-58 Phosphoric acid mono-(1,1,10-trimethyl-4,7-dioxo-10-phosphonooxy-undecyl) ester;

Ib-59 2,14-Dihydroxy-2,14-dimethyl-pentadecane-6,10-dione;

Ib-60 1,15-Dihydroxy-2,2,14,14-tetramethyl-pentadecane-6,10-dione;

Ib-61 2,2,14,14-Tetramethyl-6,10-dioxo-pentadecanedioic acid;

Ib-62 2,2,14,14-Tetramethyl-6,10-dioxo-pentadecanedial;

Ib-63 2,2,14,14-Tetramethyl-6,10-dioxo-pentadecanedioic acid dimethyl ester;

Ib-64 2,2,14,14-Tetramethyl-6,10-dioxo-hexadecanedioic acid diphenyl ester;

Ib-65 2,2,14,14-Tetramethyl-6,10-dioxo-hexadecanedioic acid dibenzyl ester;

Ib-66 2,14-Dimethyl-6,10-dioxo-pentadecane-2,14-disulfonic acid;

Ib-67 Phosphoric acid mono-(1,1,13-trimethyl-5,9-dioxo-13-phosphonooxy-tetradecyl) ester;

Ib-68 2,14-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,14-dimethyl-pentadecane-6,10-dione;

Ib-69 2,14-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,14-dimethyl-pentadecane-6,10-dione;

Ib-70 2,2,14,14-Tetramethyl-6,10-dioxo-pentadecanedioic acid dicyanimide

Ib-71 Phosphoramidic acid mono-[13-(amino-hydroxy-phosphoryloxy)-1,1,13-trimethyl-5,9-dioxo-tetradecyl] ester;

Ib-72 2,14-Dimethyl-2,14-bis-(amino-hydroxy-phosphoryloxy)-pentadecane-6,10-dione;

Ib-73 2,14-Dimethyl-2,14-bis-tetrazol-1-yl-pentadecane-6,10-dione;

Ib-74 2,14-Dimethyl-2,14-bis-(1*H*-tetrazol-5-yl)-pentadecane-6,10-dione;

Ib-75 2,14-Bis-(3-hydroxy-isoxazol-5-yl)-2,14-dimethyl-pentadecane-6,10-dione;

Ib-76 2,14-Bis-(3-hydroxy-isoxazol-4-yl)-2,14-dimethyl-pentadecane-6,10-dione;

Ib-77 2,14-Bis-(5-hydroxy-4-oxo-4*H*-pyran-3-yl)-2,14-dimethyl-pentadecane-6,10-dione;

Ib-78 2-(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)-2,14-dimethyl-14-(5-methyl-4-oxo-4*H*-pyran-2-yl)-pentadecane-6,10-dione;

Ib-79 2,14-Bis-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-2,14-dimethyl-pentadecane-6,10-dione;

Ib-80 2,14-Bis-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-2,14-dimethyl-pentadecane-6,10-dione;

Ib-81 2,14-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-2,14-dimethyl-pentadecane-6,10-dione;

Ib-82 2,14-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-2,14-dimethyl-pentadecane-6,10-dione;

Ib-83 1,14-Dihydroxy-3,3,12,12-tetramethyl-tetradecane-6,9-dione;

Ib-84 3,3,12,12-Tetramethyl-6,9-dioxo-tetradecanedioic acid;

Ib-85 3,3,12,12-Tetramethyl-6,9-dioxo-tetradecanedial;

Ib-86 3,3,12,12-Tetramethyl-6,9-dioxo-tetradecanedioic acid dimethyl ester;

Ib-87 3,3,12,12-Tetramethyl-6,9-dioxo-tetradecanedioic acid diphenyl ester;

Ib-88 3,3,12,12-Tetramethyl-6,9-dioxo-tetradecanedioic acid dibenzyl ester;

Ib-89 2,2,11,11-Tetramethyl-5,8-dioxo-dodecane-1,12-disulfonic acid;

Ib-90 Phosphoric acid mono-(2,2,11,11-tetramethyl-5,8-dioxo-12-phosphonooxy-dodecyl) ester;

Ib-91 1,12-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dione;

Ib-92 1,12-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dithione;

Ib-93 3,3,12,12-Tetramethyl-6,9-dioxo-tetradecanedioic acid dicyanimide

Ib-94 Phosphoramidic acid mono-[12-(amino-hydroxy-phosphoryloxy)-2,2,11,11-tetramethyl-5,8-dioxo-dodecyl] ester;

Ib-95 2,2,11,11-Tetramethyl-1,12-bis-(aminohydroxyphosphoryloxy)-dodecane-5,8-dione;

Ib-96 2,2,11,11-Tetramethyl-1,12-bis-(1*H*-tetrazol-5-yl)-dodecane-5,8-dione;

Ib-97 1,12-Bis-(3-hydroxy-isoxazol-5-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dione;

Ib-98 1,12-Bis-(3-hydroxy-isoxazol-4-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dione;

Ib-99 1-(5-Hydroxy-4-oxo-4*H*-pyran-3-yl)-12-(5-hydroxy-4-oxo-4*H*-pyran-2-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dione;

Ib-100 1,12-Bis-(5-hydroxy-4-oxo-4*H*-pyran-3-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dione;

Ib-101 1,12-Bis-(5-hydroxy-4-oxo-4*H*-pyran-3-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dione;

Ib-102 1-Ethyl-3-[12-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-2,2,11,11-tetramethyl-5,8-dioxo-dodecyl]-imidazolidine-2,4-dione;

Ib-103 1-Ethyl-3-[12-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-2,2,11,11-tetramethyl-5,8-dioxo-dodecyl]-imidazolidine-2,4-dione;

Ib-104 1,12-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dione;

Ib-105 1,12-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-2,2,11,11-tetramethyl-dodecane-5,8-dione;

Ib-106 1,16-Dihydroxy-4,4,13,13-tetramethyl-hexadecane-7,10-dione;

Ib-107 4,4,13,13-Tetramethyl-7,10-dioxo-hexadecanedioic acid;

Ib-108 4,4,13,13-Tetramethyl-7,10-dioxo-hexadecanedial;

Ib-109 4,4,13,13-Tetramethyl-7,10-dioxo-hexadecanedioic acid dimethyl ester;

Ib-110 4,4,13,13-Tetramethyl-7,10-dioxo-hexadecanedioic acid diphenyl ester;

Ib-111 4,4,13,13-Tetramethyl-7,10-dioxo-hexadecanedioic acid dibenzyl ester;

Ib-112 3,3,12,12-Tetramethyl-6,9-dioxo-tetradecane-1,14-disulfonic acid;

Ib-113 Phosphoric acid mono-(3,3,12,12-tetramethyl-6,9-dioxo-14-phosphonooxy-tetradecyl) ester;

Ib-114 1,14-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione;

Ib-115 1,14-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione;

Ib-116 4,4,13,13-Tetramethyl-7,10-dioxo-hexadecanedioic acid dicyanimide

Ib-117 Phosphoramidic acid mono-[14-(amino-hydroxy-phosphoryloxy)-3,3,12,12-tetramethyl-6,9-dioxo-tetradecyl] ester;

Ib-118 3,3,12,12-Tetramethyl-1,14-bis-(amino-hydroxy-phosphoryloxy)-tetradecane-6,9-dione;

Ib-119 1,12-Dihydroxy-2,2,11,11-tetramethyl-dodecane-5,8-dione;

Ib-120 2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid;

Ib-121 2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedial;

Ib-122 2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid dimethyl ester;

Ib-123 2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid diphenyl ester;

Ib-124 2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid dibenzyl ester;

Ib-125 2,11-Dimethyl-5,8-dioxo-dodecane-2,11-disulfonic acid;

Ib-126 Phosphoric acid mono-(1,1,10-trimethyl-4,7-dioxo-10-phosphonooxy-undecyl) ester;

Ib-127 2,11-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,11-dimethyl-dodecane-5,8-dione;

Ib-128 2,11-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,11-dimethyl-dodecane-5,8-dione;

Ib-129 2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid dicyanimide

Ib-130 Phosphoramidic acid mono-[10-(amino-hydroxy-phosphoryloxy)-1,1,10-trimethyl-4,7-dioxo-undecyl] ester;

Ib-131 2,2,11,11-Tetramethyl-1,12-(amino-hydroxy-phosphoryloxy)-dodecane-5,8-dione;

Ib-132 3,3,12,12-Tetramethyl-1,14-bis-tetrazol-1-yl-tetradecane-6,9-dione;

Ib-133 3,3,12,12-Tetramethyl-1,14-bis-(1*H*-tetrazol-5-yl)-tetradecane-6,9-dione;

Ib-134 1,14-Bis-(3-hydroxy-isoxazol-5-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione;

Ib-135 1,14-Bis-(3-hydroxy-isoxazol-4-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione;

Ib-136 1-(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)-14-(5-hydroxy-4-oxo-4*H*-pyran-3-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione;

Ib-137 1,14-Bis-(5-hydroxy-4-oxo-4*H*-pyran-2-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione;

Ib-138 1,14-Bis-(*5*-hydroxy-4-oxo-4*H*-pyran-3-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione;

Ib-139 1-Ethyl-3-[14-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-3,3,12,12-tetramethyl-6,9-dioxo-tetradecyl]-imidazolidine-2,4-dione;

Ib-140 1-Ethyl-3-[14-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-3,3,12,12-tetramethyl-6,9-dioxo-tetradecyl]-imidazolidine-2,4-dione;

Ib-141 1-Ethyl-3-[14-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-3,3,12,12-tetramethyl-6,9-dioxo-tetradecyl]-imidazolidine-2,4-dithione;

Ib-142 1,14-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione;

Ib-143 1,14-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dione;

Ib-144 1,17-Dihydroxy-3,3,15,15-tetramethyl-heptadecane-7,11-dione;

Ib-145 3,3,15,15-Tetramethyl-7,11-dioxo-heptadecanedial;

Ib-146 3,3,15,15-Tetramethyl-7,11-dioxo-heptadecanedioic acid dimethyl ester;

Ib-147 1,17-Dihydroxy-3,3,15,15-tetramethyl-heptadecane-7,11-dione;

Ib-148 3,3,15,15-Tetramethyl-7,11-dioxo-heptadecanedioic acid diphenyl ester;

Ib-149 3,3,15,15-Tetramethyl-7,11-dioxo-heptadecanedioic acid dibenzyl ester;

Ib-150 2,11-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,11-dimethyl-dodecane-5,8-dione;

Ib-151 2,11-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,11-dimethyl-dodecane-5,8-dione;

Ib-152 2,2,11,11-Tetramethyl-5,8-dioxo-dodecanedioic acid dicyanamide;

Ib-153 Phosphoramidic acid mono-[10-(amino-hydroxy-phosphoryloxy)-1,1,10-trimethyl-4,7-dioxo-undecyl] ester;

Ib-154 2,11-Dimethyl-2,11-bis-(amino-hydroxy-phosphoryloxy)-dodecane-5,8-dione;

Ib-155 2,11-Dimethyl-2,11-bis-tetrazol-1-yl-dodecane-5,8-dione;

Ib-156 2,11-Dimethyl-2,11-bis-(1*H*-tetrazol-5-yl)-dodecane-5,8-dione;

Ib-157 2,2,14,14-Tetramethyl-6,10-dioxo-pentadecane-1,15-disulfonic acid;

Ib-158 Phosphoric acid mono-(2,2,14,14-tetramethyl-6,10-dioxo-15-phosphonooxy-pentadecyl) ester;

Ib-159 1,15-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione;

Ib-160 1,15-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione;

Ib-161 3,3,15,15-Tetramethyl-7,11-dioxo-heptadecanedioic acid dicyanamide;

Ib-162 Phosphoramidic acid mono-[16-(amino-hydroxy-phosphoryloxy)-4,4,15,15-tetramethyl-7,11-dioxo-hexadecyl] ester;

Ib-163 2,2,14,14-Tetramethyl-1,15-bis-(amino-hydroxy-phosphoryloxy)-pentadecane-6,10-dione;

Ib-164 2,2,14,14-Tetramethyl-1,15-bis-tetrazol-1-yl-pentadecane-6,10-dione;

Ib-165 2,2,14,14-Tetramethyl-1,15-bis-(1*H*-tetrazol-5-yl)-pentadecane-6,10-dione;

Ib-166 1,15-Bis-(3-hydroxy-isoxazol-5-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione;

Ib-167 1,15-Bis-(3-hydroxy-isoxazol-4-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione;

Ib-168 1-(5-Hydroxy-4-oxo-4*H*-pyran-3-yl)-15-(5-hydroxy-4-oxo-4*H*-pyran-2-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione;

Ib-169 1,15-Bis-(5-hydroxy-4-oxo-4*H*-pyran-2-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione;

Ib-170 1,15-Bis-(5-hydroxy-4-oxo-4*H*-pyran-3-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione;

Ib-171 1,15-Bis-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione;

Ib-172 1-Ethyl-3-[15-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-2,2,14,14-tetramethyl-6,10-dioxo-pentadecyl]-imidazolidine-2,4-dione;

Ib-173 1,15-Bis-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione;

Ib-174 1,15-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione;

Ib-175 1,15-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-2,2,14,14-tetramethyl-pentadecane-6,10-dione;

Ic-1 1,9-Bis-(tetrahydro-pyran-2-yloxy)-nonane-3,7-dione;

Ic-2 1,9-Bis-(4-oxo-oxetan-2-yl)-nonane-3,7-dione;

Ic-3 1,9-Bis-(2-oxo-oxetan-3-yl)-nonane-3,7-dione;

Ic-4 1,9-Bis-(5-oxo-tetrahydrofuran-2-yl)-nonane-3,7-dione;

Ic-5 1,9-Bis-(5-oxo-tetrahydrofuran-3-yl)-nonane-3,7-dione;

Ic-6 1,9-Bis-(2-oxo-tetrahydrofuran-3-yl)-nonane-3,7-dione;

Ic-7 {2-[9-(4-Carboxymethyl-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-3,7-dioxo-nonyl]-4-hydroxy-6-oxo-tetrahydropyran-4-yl}-acetic acid;

Ic-8 1,9-Bis-(6-oxo-tetrahydropyran-2-yl)-nonane-3,7-dione;

Ic-9 1,9-Bis-(6-oxo-tetrahydropyran-3-yl)-nonane-3,7-dione;

Ic-10 1,9-Bis-(2-oxo-tetrahydropyran-4-yl)-nonane-3,7-dione;

Ic-11 1,9-Bis-(2-oxo-tetrahydropyran-3-yl)-nonane-3,7-dione;

Ic-12 1,11-Bis-(tetrahydro-pyran-2-yloxy)-undecane-4,8-dione;

Ic-13 1,11-Bis-(2-oxo-oxetan-3-yl)-undecane-4,8-dione;

Ic-14 1,11-Bis-(2-oxo-oxetan-3-yl)-undecane-4,8-dione;

Ic-15 1,11-Bis-(5-oxo-tetrahydrofuran-2-yl)-undecane-4,8-dione;

Ic-16 1,11-Bis-(5-oxo-tetrahydrofuran-3-yl)-undecane-4,8-dione;

Ic-17 1,11-Bis-(2-oxo-tetrahydrofuran-3-yl)-undecane-4,8-dione;

Ic-18 {2-[11-(4-Carboxymethyl-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-4,8-dioxo-undecyl]-4-hydroxy-6-oxo-tetrahydropyran-4-yl}-acetic acid;

Ic-19 1,11-Bis-(6-oxo-tetrahydropyran-2-yl)-undecane-4,8-dione;

Ic-20 1,11-Bis-(6-oxo-tetrahydropyran-3-yl)-undecane-4,8-dione;

Ic-21 1,11-Bis-(2-oxo-tetrahydropyran-4-yl)-undecane-4,8-dione;

Ic-22 1,11-Bis-(2-oxo-tetrahydropyran-3-yl)-undecane-4,8-dione;

Ic-23 1,8-Bis-(tetrahydropyran-2-yloxy)-octane-3,6-dione;

Ic-24 1,8-Bis-(4-oxo-oxetan-2-yl)-octane-3,6-dione;

Ic-25 1,8-Bis-(2-oxo-oxetan-3-yl)-octane-3,6-dione;

Ic-26 1,8-Bis-(5-oxo-tetrahydro-furan-2-yl)-octane-3,6-dione;

Ic-27 1,8-Bis-(5-oxo-tetrahydro-furan-3-yl)-octane-3,6-dione;

Ic-28 1,8-Bis-(2-oxo-tetrahydro-furan-3-yl)-octane-3,6-dione;

Ic-29 {2-[8-(4-Carboxymethyl-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-3,6-dioxo-octyl]-4-hydroxy-6-oxo-tetrahydro-pyran-4-yl}-acetic acid;

Ic-30 1,8-Bis-(6-oxo-tetrahydropyran-2-yl)-octane-3,6-dione;

Ic-31 1,8-Bis-(6-oxo-tetrahydropyran-3-yl)-octane-3,6-dione;

Ic-32 1,8-Bis-(2-oxo-tetrahydropyran-4-yl)-octane-3,6-dione;

Ic-33 1,8-Bis-(2-oxo-tetrahydropyran-3-yl)-octane-3,6-dione;

II-1 1,13-Dihydroxy-2,2,12,12-tetramethyl-tridecan-7-one;

II-2 13-Hydroxy-2,2,12,12-tetramethyl-7-oxo-tridecanoic acid;

II-3 2,2,12,12-Tetramethyl-7-oxo-tridecanedioic acid;

II-4 1,11-Dihydroxy-2,2,10,10-tetramethyl-undecan-6-one;

II-5 11-Hydroxy-2,2,10,10-tetramethyl-6-oxo-undecanoic acid;

II-6 2,2,10,10-Tetramethyl-6-oxo-undecanedioic acid;

II-7 1,15-Dihydroxy-2,2,14,14-tetramethyl-pentadecan-8-one;

II-8 15-Hydroxy-2,2,14,14-tetramethyl-8-oxo-pentadecanoic acid;

II-9 2,2,14,14-Tetramethyl-8-oxo-pentadecanedioic acid;

II-10 2,2,12,12-Tetramethyl-7-oxo-tridecanedial;

II-11 2,2,12,12-Tetramethyl-7-oxo-tridecanedioic acid dimethyl ester;

II-12 2,2,12,12-Tetramethyl-1,13-diphenyl-tridecane-1,7,13-trione;

II-13 3,3,13,13-Tetramethyl-1,15-diphenyl-pentadecane-2,8,14-trione;

II-14 2,12-Dimethyl-7-oxo-tridecane-2,12-disulfonic acid;

II-15 Phosphoric acid mono-(1,1,11-trimethyl-6-oxo-11-phosphonooxy-dodecyl) ester;

II-16 2,2,14,14-Tetramethyl-8-oxo-pentadecanedial;

II-17 2,2,14,14-Tetramethyl-8-oxo-pentadecanedioic acid dimethyl ester;

II-18 2,2,14,14-Tetramethyl-1,15-diphenyl-pentadecane-1,8,15-trione;

II-19 3,3,15,15-Tetramethyl-1,17-diphenyl-heptadecane-2,9,16-trione;

II-20 2,14-Dimethyl-8-oxo-pentadecane-2,14-disulfonic acid;

II-21 Phosphoric acid mono-(1,1,13-trimethyl-7-oxo-13-phosphonooxy-tetradecyl) ester;

II-22 1,15-Dihydroxy-3,3,13,13-tetramethyl-pentadecan-8-one;

II-23 15-Hydroxy-3,3,13,13-tetramethyl-8-oxo-pentadecanoic acid;

II-24 1,13-Dihydroxy-3,3,11,11-tetramethyl-tridecan-7-one;

II-25 1,13-Dihydroxy-3,3,11,11-tetramethyl-tridecan-7-one;

II-26 13-Hydroxy-3,3,11,11-tetramethyl-7-oxo-tridecanoic acid;

II-27 3,3,11,11-Tetramethyl-7-oxo-tridecanedioic acid;

II-28 1,17-Dihydroxy-3,3,15,15-tetramethyl-heptadecan-9-one;

II-29 17-Hydroxy-3,3,15,15-tetramethyl-9-oxo-heptadecanoic acid;

II-30 3,3,15,15-Tetramethyl-9-oxo-heptadecanedioic acid;

II-31 1,17-Dihydroxy-4,4,14,14-tetramethyl-heptadecan-9-one;

II-32 17-Hydroxy-4,4,14,14-tetramethyl-9-oxo-heptadecanoic acid;

II-33 4,4,14,14-Tetramethyl-heptadecan-9-oxo-1,17-dicarboxylic acid;

II-34 1,15-Dihydroxy-4,4,14,14-tetramethyl-pentadecan-8-one;

II-35 15-Hydroxy-4,4,12,12-tetramethyl-8-oxo-pentadecanoic acid;

II-36 4,4,12,12-Tetramethyl-8-oxo-pentadecanedioic acid;

II-37 1,19-Dihydroxy-4,4,16,16-tetramethyl-nonadecan-10-one;

II-38 19-Hydroxy-4,4,16,16-tetramethyl-10-oxo-nonadecanoic acid;

II-39 4,4,16,16-Tetramethyl-10-oxo-nonadecanedioic acid;

II-40 2,10-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,10-dimethyl-undecan-6-one;

II-41 2,10-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,10-dimethyl-undecan-6-one;

II-42 2,2,10,10-Tetramethyl-6-oxo-undecanedioic acid bis-cyanamide;

II-43 Phosphoramidic acid mono-[9-(amino-hydroxy-phosphoryloxy)-1,1,9-trimethyl-5-oxo-decyl] ester;

II-44 Phosphoramidic acid mono-[9-(amino-hydroxy-phosphoryloxy)-1,1,9-trimethyl-5-oxo-decyl] ester;

II-45 2,12-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,12-dimethyl-tridecan-7-one;

II-46 2,12-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,12-dimethyl-tridecan-7-one;

II-47 2,2,12,12-Tetramethyl-7-oxo-tridecanedioic acid bis-cyanamide;

II-48 Phosphoramidic acid mono-[11-(amino-hydroxy-phosphoryloxy)-1,1,11-trimethyl-6-oxo-dodecyl] ester;

II-49 Phosphoramidic acid mono-[11(amino-hydroxy-phosphoryloxy)-1,1,11-trimethyl-6-oxo-dodecyl] ester;

II-50 2,12-Dimethyl-2,12-bis-tetrazol-1-yl-tridecan-7-one;

II-51 2,12-Dimethyl-2,12-bis-(1*H*-tetrazol-5-yl)-tridecan-7-one;

II-52 2,12-Bis-(3-hydroxy-isoxazol-5-yl)-2,12-dimethyl-tridecan-7-one;

II-53 2,12-Bis-(3-hydroxy-isoxazol-4-yl)-2,12-dimethyl-tridecan-7-one;

II-54 4-[11-(4-oxo-oxetan-2-yl)-1,1,11-Trimethyl-6-oxo-dodecyl]-oxetan-2-one;

II-55 3-[11-(4-oxo-oxetan-2-yl)-1,1,11-Trimethyl-6-oxo-dodecyl]-oxetan-2-one;

II-56 5-[11-(5-oxo-tetrahydro-furan-3-yl)-1,1,11-Trimethyl-6-oxo-dodecyl]-dihydro-furan-2-one;

II-57 3-[11-(5-oxo-tetrahydro-furan-3-yl)-1,1,11-Trimethyl-6-oxo-dodecyl]-dihydro-furan-2-one;

II-58 4-[11-(5-oxo-tetrahydro-furan-3-yl)-1,1,11-Trimethyl-6-oxo-dodecyl]-dihydro-furan-2-one;

II-59 2,12-Dimethyl-2,12-bis-(tetrahydro-pyran-2-yloxy)-tridecan-7-one;

II-60 {2-[9-(4-Carboxymethyl-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-1,1,9-trimethyl-5-oxo-decyl]-4-hydroxy-6-oxo-tetrahydro-pyran-4-yl}-acetic acid;

IIa-1 1,15-Dihydroxy-2,14-dimethyl-2,14-diphenyl-pentadecan-8-one;

IIa-2 15-Hydroxy-2,14-dimethyl-8-oxo-2,14-diphenyl-pentadecanoic acid;

IIa-3 2,14-Dimethyl-8-oxo-2,14-diphenyl-pentadecanedioic acid;

IIa-4 1,13-Dihydroxy-2,12-dimethyl-2,12-diphenyl-tridecan-7-one;

IIa-5 13-Hydroxy-2,12-dimethyl-7-oxo-2,12-diphenyl-tridecanoic acid;

IIa-6 2,12-Dimethyl-7-oxo-2,12-diphenyl-tridecanedioic acid;

IIa-7 1,11-Dihydroxy-2,10-dimethyl-2,10-diphenyl-undecan-6-one;

IIa-8 11-Hydroxy-2,10-dimethyl-6-oxo-2,10-diphenyl-undecanoic acid;

IIa-9 2,10-Dimethyl-6-oxo-2,10-diphenyl-undecanedioic acid;

IIa-10 2,14-Dimethyl-8-oxo-2,14-diphenyl-pentadecanedial;

IIa-11 2,14-Dimethyl-8-oxo-2,14-diphenyl-pentadecanedioic acid dimethyl ester;

IIa-12 2,14-Dimethyl-1,2,14,15-tetraphenyl-pentadecane-1,8,15-trione;

IIa-13 3,15-Dimethyl-1,3,15,17-tetraphenyl-heptadecane-2,9,16-trione;

IIa-14 8-Oxo-2,14-diphenyl-pentadecane-2,14-disulfonic acid;

IIa-15 Phosphoric acid mono-(1-methyl-7-oxo-1,13-diphenyl-13-phosphonooxy-tetradecyl) ester;

IIa-16 1,17-Dihydroxy-3,15-dimethyl-3,15-diphenyl-heptadecan-9-one;

IIa-17 17-Hydroxy-3,15-dimethyl-9-oxo-3,15-diphenyl-heptadecanoic acid;

IIa-18 3,15-Dimethyl-9-oxo-3,15-diphenyl-heptadecanedioic acid;

IIa-19 1,15-Dihydroxy-3,13-dimethyl-3,13-diphenyl-pentadecan-8-one;

IIa-20 15-Hydroxy-3,13-dimethyl-8-oxo-3,13-diphenyl-pentadecanoic acid;

IIa-21 3,13-Dimethyl-8-oxo-3,13-diphenyl-pentadecanedioic acid;

IIa-22 1,13-Dihydroxy-3,11-dimethyl-3,11-diphenyl-tridecan-7-one;

IIa-23 13-Hydroxy-3,11-dimethyl-7-oxo-3,11-diphenyl-tridecanoic acid;

IIa-24 3,11-Dimethyl-7-oxo-3,11-diphenyl-tridecanedioic acid;

IIa-25 13-Hydroxy-3,11-dimethyl-7-oxo-3,11-diphenyl-tridecanoic acid;

IIa-26 3,11-Dimethyl-7-oxo-3,11-diphenyl-tridecanedioic acid;

IIa-27 1,19-Dihydroxy-4,16-dimethyl-4,16-diphenyl-nonadecan-10-one;

IIa-28 19-Hydroxy-4,16-dimethyl-10-oxo-4,16-diphenyl-nonadecanoic acid;

IIa-29 4,16-Dimethyl-10-oxo-4,16-diphenyl-nonadecanedioic acid;

IIa-30 1,17-Dihydroxy-4,14-dimethyl-4,14-diphenyl-heptadecan-9-one;

IIa-31 17-Hyclroxy-4,14-dimethyl-9-oxo-4,14-diphenyl-heptadecanoic acid;

IIa-32 4,14-Dimethyl-9-oxo-4,14-diphenyl-heptadecanedioic acid;

IIa-33 1,15-Dihydroxy-4,12-dimethyl-4,12-diphenyl-pentadecan-8-one;

IIa-34 15-Hydroxy-4,12-dimethyl-8-oxo-4,12-diphenyl-pentadecanoic acid;

IIa-35 4,12-Dimethyl-8-oxo-4,12-diphenyl-pentadecanedioic acid;

IIa-36 2,12-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,12-diphenyl-tridecan-7-one;

IIa-37 2,12-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4*H*-thieno[3,2-c]pyridin-5-yl)-2,12-diphenyl-tridecan-7-one;

IIa-38 2,12-Dimethyl-2,12-diphenyl-7-oxo-tridecanedioic acid bis-cyanamide;

IIa-39 Phosphoramidic acid mono-(amino-hydroxy-phosphoryloxy)-1-methyl-6-oxo-1,11-diphenyl-dodecyl] ester;

IIa-40 Phosphoramidic acid mono-[11(amino-hydroxy-phosphoryloxy)-1,11-dipehnyl-1-methyl-6-oxo-dodecyl] ester;

IIa-41 2,12-Diphenyl-2,12-bis-tetrazol-1-yl-tridecan-7-one;

IIa-42 2,12-Diphenyl-2,12-bis-(1*H*-tetrazol-5-yl)-tridecan-7-one;

IIa-43 2,12-Bis-(3-hydroxy-isoxazol-5-yl)-2,12-diphenyl-tridecan-7-one;

IIa-44 2,12-Bis-(3-hydroxy-isoxazol-4-yl)-2,12-diphenyl-tridecan-7-one;

IIa-45 2,12-Diphenyl-2,12-bis-(tetrahydro-pyran-2-yloxy)-tridecan-7-one;

IIa-46 5-[11-(5-oxo-tetrahydro-furan-2-yl)-1,11-Diphenyl-1-methyl-6-oxo-dodecyl]-dihydro-furan-2-one;

IIa-47 4-[11-(4-oxo-oxetan-2-yl)-1,11-diphenyl-1-methyl-6-oxo-dodecyl]-oxetan-2-one;

IIa-48 4-[11-(5-oxo-tetrahydro-furan-2-yl)-1,11-Diphenyl-1-methyl-6-oxo-dodecyl]-dihydro-furan-2-one;

IIa-49 3-[11-(5-oxo-tetrahydro-furan-2-yl)-1,11-Diphenyl-1-methyl-6-oxo-dodecyl]-dihydro-furan-2-one;

IIa-50 {2-[11-(4-Carboxymethyl-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-1-methyl-6-oxo-1,11-diphenyl-dodecyl]-4-hydroxy-6-oxo-tetrahydro-pyran-4-yl}-acetic acid;

III-1 5-(6-{3-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-propyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentan-1-ol;

III-2 5-(6-{3-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-propyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-3 5-(6-{3-[6-(4-Carboxy-4-methyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-propyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-4 5-(6-{3-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-propyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentan-1-ol;

III-5 5-(6-{3-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-propyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-6 5-(6-{3-[6-(4-Carboxy-4-methyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-propyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-7 6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-propyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexan-1-ol;

III-8 6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-propyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-9 6-(6-{3-[6-(5-Carboxy-5-methyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-propyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-10 6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-propyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexan-1-ol;

III-11 6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-propyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-12 6-(6-{3-[6-(5-Carboxy-5-methyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-propyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-13 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-vinyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexan-1-ol;

III-14 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-vinyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexanoic acid;

III-15 6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-1-oxo-cyclohexan-2-yl]-vinyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexanoic acid;

III-16 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-vinyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexan-1-ol;

III-17 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-vinyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-18 6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-vinyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-19 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-vinyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexan-1-ol;

III-20 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-vinyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-21 6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-vinyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-22 5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclohexan-2-yl]-vinyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentan-1-ol;

III-23 5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclohexan-2-yl]-vinyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentanoic acid;

III-24 5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclohexan-2-yl]-vinyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentanoic acid;

III-25 5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-vinyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentan-1-ol;

III-26 5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-vinyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-27 5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-vinyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-28 5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-vinyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentan-1-ol;

III-29 5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-vinyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-30 5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-vinyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-31 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-ethyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexan-1-ol;

III-32 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-ethyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-33 6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-ethyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-34 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-ethyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexan-1-ol;

III-35 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-ethyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-36 6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-ethyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-37 5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-ethyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentan-1-ol;

III-38 5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-ethyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-39 5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-ethyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-40 5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-ethyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentan-1-ol;

III-41 5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-ethyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-42 5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-ethyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-43 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-phenyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexan-1-ol;

III-44 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-phenyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexanoic acid;

III-45 6-(6-{2-[6-(6-Carboxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-phenyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexanoic acid;

III-46 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-phenyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexan-1-ol;

III-47 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-phenyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-48 6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-1,4-dioxo-cyclohexadien-2-yl]-phenyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-49 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-phenyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexan-1-ol;

III-50 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-phenyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-51 6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-phenyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-52 5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclohexan-2-yl]-phenyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentan-1-ol;

III-53 5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclohexan-2-yl]-phenyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentanoic acid;

III-54 5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclohexan-2-yl]-phenyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentanoic acid;

III-55 5-(6-{2-[6-(5-Hydroxy-4-methyl-pentyl)-1,4-dioxo-cyclohex-2-yl]-phenyl}-1,4-dioxo-cyclohex-2-yl)-2,2-dimethyl-pentan-1-ol;

III-56 5-(6-{2-[6-(5-Hydroxy-4-methyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-phenyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-57 5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-1,4-dioxo-cyclohexadien-2-yl]-phenyl}-1,4-dioxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-58 5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-phenyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentan-1-ol;

III-59 5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-phenyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-60 5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-4,4-dimethyl-1-oxo-cyclohexadien-2-yl]-phenyl}-4,4-dimethyl-1-oxo-cyclohexadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-61 5-(5-{3-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentadien-2-yl]-propyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentan-1-ol;

III-62 5-(5-{3-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentadien-2-yl]-propyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-63 5-(5-{3-[5-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclopentadien-2-yl]-propyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-64 6-(5-{3-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentadien-2-yl]-propyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexan-1-ol;

III-65 6-(5-{3-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentadien-2-yl]-propyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-66 6-(5-{3-[5-(5-Carboxy-5-methyl-hexyl)-1-oxo-cyclopentadien-2-yl]-propyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-67 6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-hexan-1-ol;

III-68 6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-hexanoic acid;

III-69 6-(5-{2-[5-(5-Carboxy-5-methyl-hexyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-hexanoic acid;

III-70 6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexan-1-ol;

III-71 6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-72 6-(5-{2-[5-(5-Carboxy-5-methyl-hexyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-73 5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-pentan-1-ol;

III-74 5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-pentanoic acid;

III-75 5-(5-{2-[5-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-pentanoic acid;

III-76 5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentan-1-ol;

III-77 5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-78 5-(5-{2-[5-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-79 6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-hexan-1-ol;

III-80 6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-hexanoic acid;

III-81 6-(5-{2-[5-(5-Carboxy-5-methyl-hexyl)-1-oxo-cyclopentan-2-yl]-vinyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-hexanoic acid;

III-82 6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexan-1-ol;

III-83 6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-84 6-(5-{2-[5-(5-Carboxy-5-methyl-hexyl)-1-oxo-cyclopentadien-2-yl]-vinyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-hexanoic acid;

III-85 5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentadien-2-yl]-ethyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentan-1-ol;

III-86 5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentadien-2-yl]-ethyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentanoic acid;

III-87 5-(5-{2-[5-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclopentadien-2-yl]-ethyl}-1-oxo-cyclopentadien-2-yl)-2,2-dimethyl-pentanoic acid;

IIIa-1 5-(6-{3-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclohexan-2-yl]-propyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentan-1-ol;

IIIa-2 5-(6-{3-[6-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclohexan-2-yl]-propyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentanoic acid;

IIIa-3 5-(6-{3-[6-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclohexan-2-yl]-propyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentanoic acid;

IIIa-4 6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-propyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexan-1-ol;

IIIa-5 6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-propyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexanoic acid;

IIIa-6 6-(6-{3-[6-(5-Carboxy-5-methyl-hexyl)-1-oxo-cyclohexan-2-yl]-propyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexanoic acid;

IIIa-7 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-ethyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexan-1-ol;

IIIa-8 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-1-oxo-cyclohexan-2-yl]-ethyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexanoic acid;

IIIa-9 6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-1-oxo-cyclohexan-2-yl]-ethyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-hexanoic acid;

IIIa-10 5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclohexan-2-yl]-ethyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentan-1-ol;

IIIa-11 5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclohexan-2-yl]-ethyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentanoic acid;

IIIa-12 5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclohexan-2-yl]-ethyl}-1-oxo-cyclohexan-2-yl)-2,2-dimethyl-pentanoic acid;

IIIa-13 5-(5-{3-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentan-2-yl]-propyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-pentan-1-ol;

IIIa-14 5-(5-{3-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-1-oxo-cyclopentan-2-yl]-propyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-pentanoic acid; or

IIIa-15 5-(5-{3-[5-(4-Carboxy-4-methyl-pentyl)-1-oxo-cyclopentan-2-yl]-propyl}-1-oxo-cyclopentan-2-yl)-2,2-dimethyl-pentanoic acid.

36. A pharmaceutical composition comprising a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35 and a pharmaceutically acceptable vehicle, excipient, or diluent.

37. A pharmaceutical composition comprising the following compound: 6-(5,5-Dimethyl-6-hydroxy-hexane-1-sulfinyl)-2,2-dimethyl-hexan-1-ol or pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates, or mixures of stereoisomers thereof and a pharmaceutically acceptable vehicle, excipient, or diluent.

38. A method for treating or preventing a cardiovascular disease in a patient, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

39. A method for treating or preventing a dyslipidemia in a patient, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

40. A method for treating or preventing a dyslipoproteinemia in a patient, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35 .

41. A method for treating or preventing a disorder of glucose metabolism in a patient, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

42. A method for treating or preventing Alzheimer's Disease in a patient, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

43. A method for treating or preventing Syndrome X or Metabolic Syndrome in a patient, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

44. A method for treating or preventing septicemia in a patient, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

45. A method for treating or preventing a thrombotic disorder in a patient, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

46. A method for treating or preventing a peroxisome proliferator activated receptor associated disorder in a patient, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

47. A method for treating or preventing obesity in a patient, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

48. A method for treating or preventing pancreatitis in a patient, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

49. A method for treating or preventing hypertension in a patient, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

50. A method for treating or preventing renal disease in a patient, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

51. A method for treating or preventing cancer in a patient, comprising administering to a patient in claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

52. A method for treating or preventing inflammation in a patient, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

53. A method for treating or preventing impotence in a patient, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

54. A method for reducing the fat content of meat in livestock comprising administering to livestock in need of such reduction a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

55. A method for reducing the cholesterol content of fowl eggs comprising administering to a fowl a therapeutically effective amount of a compound of claim 1, 9, 15, 18, 20, 21, 26, 31 or 35.

Figure 1

Effect of One Week of Daily Oral Gavage Treatment with Compound B on Lipoprotein Total Cholesterol in Chow-Fed Male Sprague-Dawly Rats

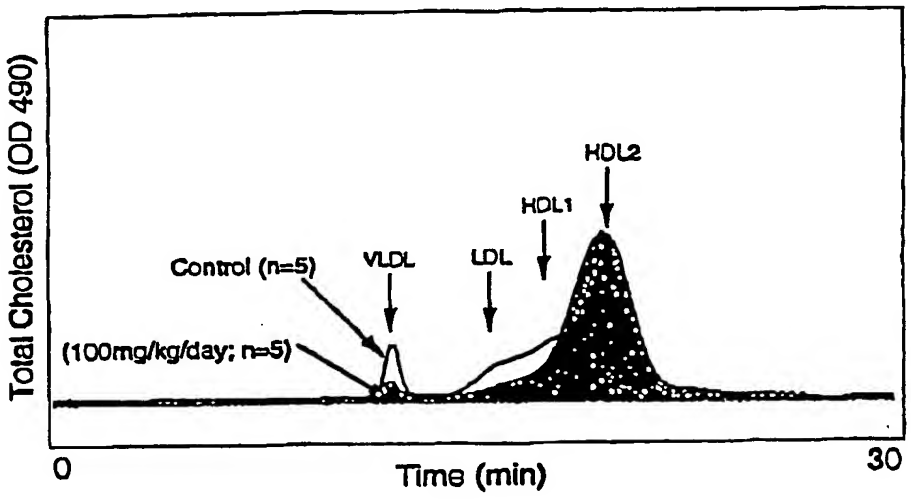


Figure 2

Effect of One Week of Daily Oral Gavage Treatment with Compound B on Serum Lipids in Chow-Fed Male Sprague-Dawly Rats

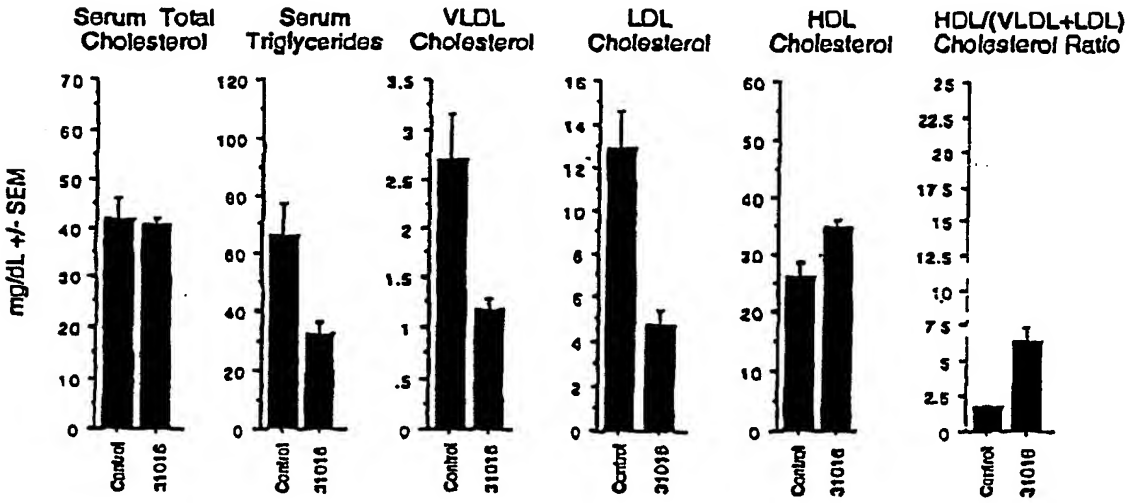


Figure 3

Effect of Two Weeks of Daily Oral Gavage Treatment with Compound B on Lipoprotein Total Cholesterol in Chow Fed Obese Female Zucker Rats

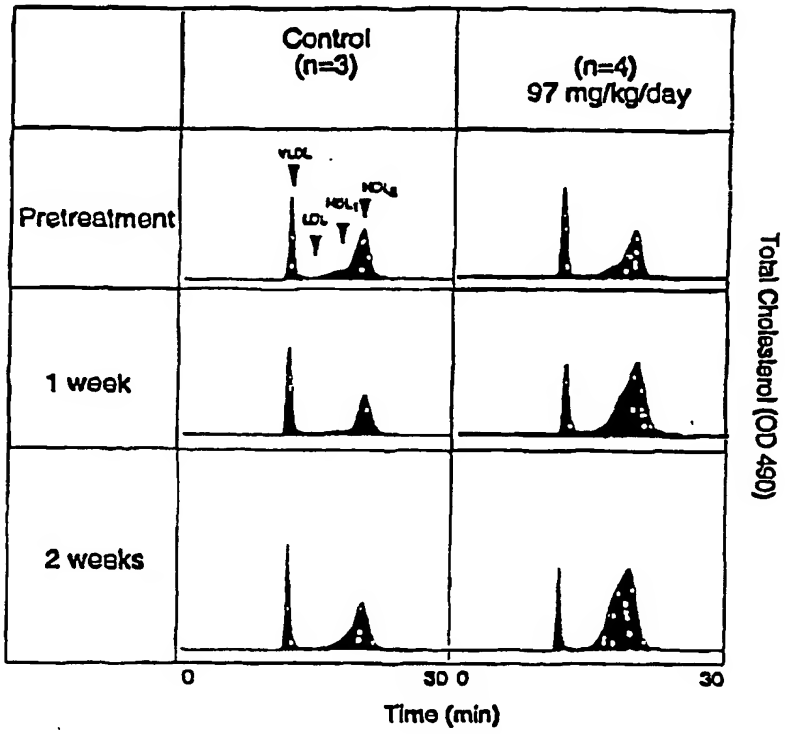


Figure 4

Effect of Two Weeks of Daily Oral Gavage Treatment with Compound B in Chow-Fed Obese Female Zucker Rats

Variable	Units	Control n=3			Compound B n=4 97/mg/kg/day		
		Pre	1 Week	2 Week	Pre	1 Week	2 Week
14 Day Percent Weight Gain	Percent	0		13.6	0		14.6
Liver/Body Weight	Percent			4.09			5.70
Blood Glucose	mg/dL	122	98	130	108	116	120
Insulin	ng/mL	12.2	8.7	6.2	10.0	8.7	8.7
Non-Esterified Fatty Acids	mmol/L	1.95	1.27	1.21	2.13	0.60	0.57
β-hydroxy butyrate	mg/dL	2.29	1.62	2.90	1.44	2.56	3.97
Total Cholesterol	mg/dL	62	56	68	59	93	112
Percent HDL Cholesterol (Gain/Loss)	Percent	0	-10	10	0	58	90
VLDL plus LDL Cholesterol	mg/dL	21	26	27	21	17	19
HDL Cholesterol	mg/dL	42	30	41	38	76	93
Percent HDL Cholesterol (Gain/Loss)	Percent	0	-28	0	0	99	143
HDL / (VLDL plus LDL)	Ratio	2.32	1.30	1.77	1.97	4.85	5.47
Triglycerides	mg/dL	999	984	887	861	299	324
Triglycerides (Gain/Loss)	Percent	0	-2	-11	0	-65	-82

Figure 5

14C-Acetate Incorporation into Saponified and non-Saponified Lipids